PDE4B INHIBITOR, AND PHARMACEUTICAL COMPOSITION THEREOF AND USE THEREOF

The present application claims priority to the following prior applications: the Chinese Patent Application No. 202410144764.1 filed with China National Intellectual Property Administration on February 1, 2024 and entitled "PDE4B INHIBITOR, PHARMACEUTICAL COMPOSITION THEREOF, AND USE THEREOF"; and the Chinese Patent Application No. 202410637006.3 filed with China National Intellectual Property Administration on May 21, 2024 and entitled "PDE4B INHIBITOR, PHARMACEUTICAL COMPOSITION THEREOF, AND USE THEREOF", which are incorporated herein by reference in their entireties.

TECHNICAL FIELD

The present disclosure relates to a PDE4B inhibitor, a pharmaceutical composition thereof, and use thereof, and pertains to the field of chemical pharmaceuticals.

BACKGROUND

Fibrosis is a general term for a large class of diseases that may occur in almost all human tissues. The fibrotic tissues and organs gradually lose their normal functions, seriously affecting the quality of life of patients and even endangering the lives of the patients. Taking pulmonary fibrosis as an example, the fibrotic tissues lose their original elasticity, making the expansion and contraction of the lungs during respiration increasingly difficult. As a result, the lung capacity decreases, and the mobility of patients can be severely compromised.

Idiopathic pulmonary fibrosis (IPF) is a progressive pulmonary fibrosis disease characterized by rapid progression, often leading to patient mortality within just a few years; indeed, its prognosis is even poorer than that of many cancers. Due to the increasing severity of lung fibrosis and unpredictability of disease progression, IPF patients suffer from the unimaginable "pain of breathlessness" and may die at any time from respiratory failure and/or heart failure. Meanwhile, most IPF patients have atypical clinical manifestations and are prone to missed diagnosis, and are often misdiagnosed as chronic obstructive pulmonary disease, bronchial asthma, or other pulmonary diseases. The median survival time of the patients diagnosed with IPF is only 2.5 to 5 years.

IPF is defined as a rare disease in China, the European Union, the United States, and Japan, and there are about 3 million IPF patients worldwide. The disease primarily involves patients

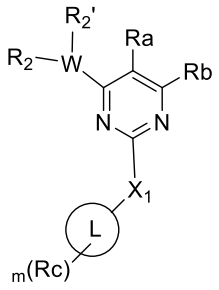
over 50 years of age, with more males than females. Large-scale epidemiological study data on the incidence of IPF in China remain unavailable. Nevertheless, on the basis of China's massive population base, the disease burden imposed by IPF on individuals, families, society, and public health resources is substantial and cannot be overlooked.

The PDE4 subfamily includes four subtypes (PDE4A, PDE4B, PDE4C, and PDE4D), and different subtypes have different tissue distributions: PDE4A is ubiquitous and is relatively highly expressed in adipose tissue, brain, heart, and testis; PDE4B is also widely distributed and is particularly expressed at high levels in lung, immune cells, brain, heart, and skeletal muscle; PDE4C is mainly expressed in testis and other tissues, with low expression in lung and no expression in blood and immune cells; and PDE4D is mainly expressed in brain, immune cells, and skeletal muscle cells. It can be seen that the PDE4B subtype is expressed at a higher level in the lungs than the other subtypes. In vitro studies targeting PDE4B in pulmonary fibrosis have demonstrated that the inhibition of PDE4B has important roles in anti-inflammation and anti-fibrosis. The inhibition of PDE4B can lead to an increase in the intracellular cAMP level, which in turn activates protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC), reducing the synthesis and release of pro-inflammatory cytokines and promoting the synthesis of anti-inflammatory cytokines.

Although there is preclinical evidence suggesting that PDE4 inhibitors are associated with anti-inflammatory and anti-fibrotic effects that may reduce inflammation and fibrotic remodeling in pulmonary diseases, many PDE4 inhibitors cause gastrointestinal side effects due to their poor selectivity, resulting in the termination of clinical trials. Therefore, there is a need to develop PDE4B inhibitors that exhibit better selectivity and/or lower gastrointestinal side effects.

SUMMARY

In view of the above technical problems, the present disclosure provides a compound represented by formula H below, or a racemate, a stereoisomer, a tautomer, an isotopically labeled compound, a solvate, a polymorph, a metabolite, a pharmaceutically acceptable salt, or a prodrug thereof:



H

wherein:

X_1 represents a chemical bond, C_{1-20} alkylene, O, S, NR_q, S(=O), $S(=O)_2$, or C(=O);

R_q is selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, C_{1-8} heteroalkyl-fused C_{6-20} aryl-, C_{1-8} heteroalkyl-C_{6-20} aryl-, NH_2, $-C(O)R_{41}$, $-C(O)OR_{42}$, $-OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

L represents a chemical bond, C_{2-20} alkynyl, or Cy, wherein L may be linked to X_1 or R_c at any position;

Cy represents 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl, wherein the 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl may be optionally fused to 4- to 7-membered cycloalkyl, provided that when the heterocyclyl contains an N atom, the heterocyclyl may be bonded to the carbon atom at the 2-position of the pyrimidine ring in formula H via the N atom or a C atom thereof;

W represents a chemical bond, CH, O, S, N, -S(O)-, $-S(O)_2-$, -C(O), C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene;

R_2 is absent or selected from H and the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d1}: C_{6-20} aryl and 5- to 20-membered heteroaryl;

$R_{2'}$ is absence or represents H, halogen, OH, CN, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d2}: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered

heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, and NH_2;

provided that R_2 and $R_{2'}$ are not both "absent";

or alternatively, R_2 and $R_{2'}$, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d3}: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and 6- to 20-membered aryl;

R_a represents H or -X-R_3;

X represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_3 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d4}: C_{1-20} alkyl, -C(O)R_{61}, -C(O)OR_{62}, -OC(O)R_{63}, and NH_2;

R_b represents H or -Y-R_4;

Y represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_4 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d5}: C_{1-20} alkyl, -C(O)R_{61}, -C(O)OR_{62}, -OC(O)R_{63}, and NH_2;

provided that R_a and R_b are not both H;

or R_a and R_b, together with the atoms linked thereto, form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d6}: C_{5-20} cycloalkenyl, 3- to 20-membered heterocyclyl, 5- to 20-membered heteroaryl, and 6- to 20-membered aryl;

R_{d1}, R_{d2}, R_{d3}, R_{d4}, R_{d5}, and R_{d6} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), SO, SO_2, and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, -C(O)R_{31}, -CH_2-C(O)R_{31}, -C(O)OR_{32}, -CH_2C(O)OR_{32}, -C(O)NHR_{32}, -CH_2C(O)NHR_{32}, -OC(O)R_{33}, -$S(O)_2R_{34}$, -$S(O)_2OR_{35}$, -$OS(O)_2R_{36}$, and -P(O)(OR_{37})(OR_{38});

or when two or more substituents selected from R_{d1}, R_{d2}, R_{d3}, R_{d4}, R_{d5}, and R_{d6} are present on

the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_c are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl-O-C_{6-20} aryl-, 5- to 20-membered heteroaryl-N-C_{6-20} aryl-, 5- to 20-membered heteroaryl-S-C_{6-20} aryl-, 5- to 20-membered heteroaryl-CH_2-C_{6-20} aryl-, C_{4-10} cycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-fused C_{6-20} aryl-, C_{4-10} cycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl, C_{4-10} cycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-fused 5- to 20-membered heteroaryl-, C_{4-10} cycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-5- to 20-membered heteroaryl-, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, -C(O)R_{31}, -C(O)OR_{32}, -OC(O)R_{33}, -S(O)$_2R_{34}$, -S(O)$_2$OR_{35}, -OS(O)$_2R_{36}$, and -P(O)(OR_{37})(OR_{38});

m is selected from integers from 1 to 10;

R_e are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, NH_2, oxo (=O), thio (=S), O-$CONH_2$, O-$CONHR_f$, and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, C_{1-8} heteroalkyl-fused C_{6-20} aryl-, C_{1-8} heteroalkyl-C_{6-20} aryl-, NH_2, -C(O)R_{41}, -C(O)OR_{42}, -

$OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

or when two or more substituents selected from R_e are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_f are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{51}$, $-C(O)OR_{52}$, $-OC(O)R_{53}$, $-S(O)_2R_{54}$, $-S(O)_2OR_{55}$, $-OS(O)_2R_{56}$, and $-P(O)(OR_{57})(OR_{58})$;

or when two or more substituents selected from R_f are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_g are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, and R_{58} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

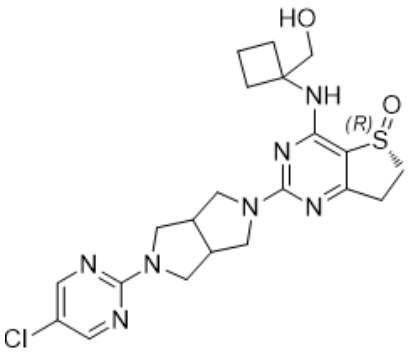
the 3- to 20-membered heterocyclyl represents a saturated or unsaturated non-aromatic ring or ring system; for example, it is a 4-, 5-, 6-, or 7-membered monocyclic ring system, a 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic (e.g., fused, bridged, or spiro) ring system, or a 10-, 11-, 12-, 13-, 14-, or 15-membered tricyclic ring system, and contains at least one, e.g., 1, 2, 3, 4, 5, or

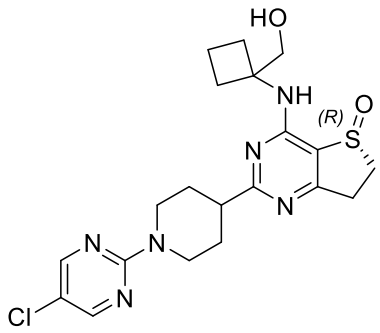
more heteroatoms independently selected from O, S, and N, wherein N and S may also be optionally oxidized to various oxidized forms to form nitrogen oxides, -S(O)-, or -$S(O)_2$-;

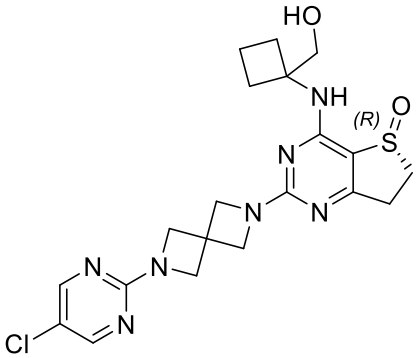
the C_{6-20} aryl represents an aromatic or partially aromatic monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic hydrocarbon ring having 6-20 carbon atoms, which may be a single aromatic ring or multiple aromatic rings fused together;

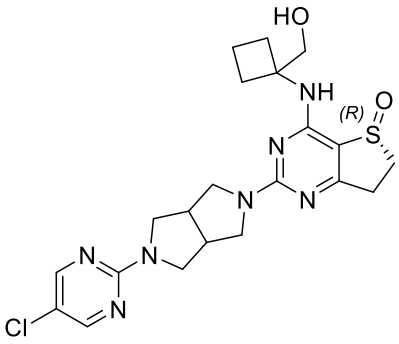
the 5- to 20-membered heteroaryl represents a monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic aromatic ring system, wherein the aromatic ring system has 5-20 ring atoms and contains 1, 2, 3, 4, 5, or more heteroatoms independently selected from N, O, and S.

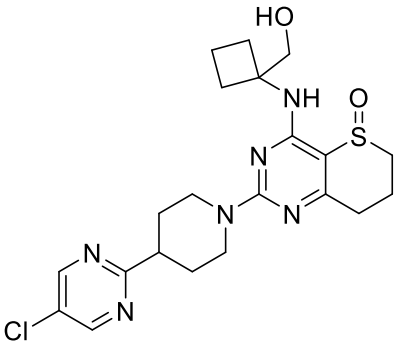
According to a preferred embodiment in the context of the present disclosure, the compound does not comprise a compound and/or a stereoisomer thereof and/or a racemate thereof selected from:

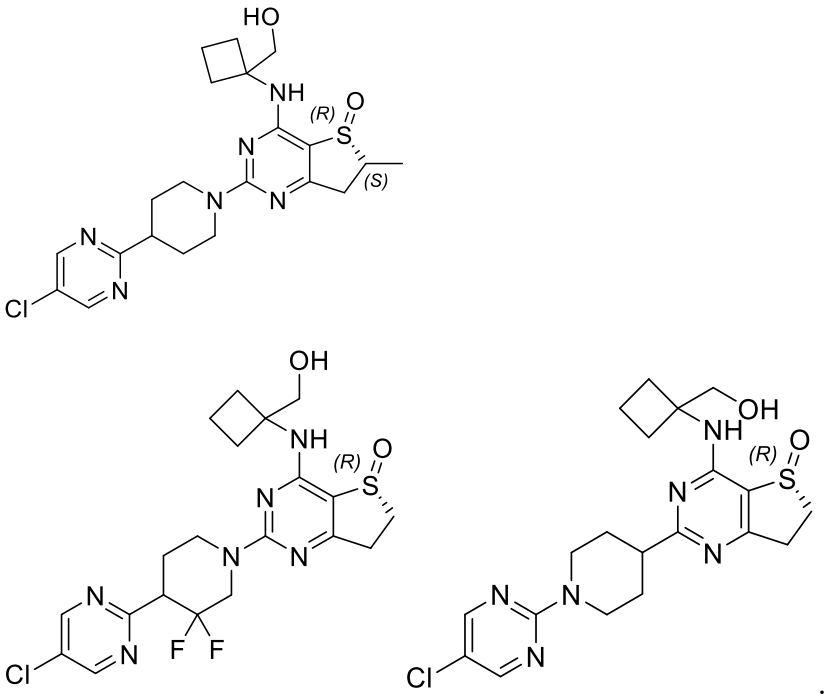




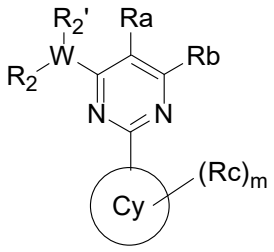








According to an embodiment of the present disclosure, the present disclosure provides a compound represented by formula G below, or a racemate, a stereoisomer, a tautomer, an isotopically labeled compound, a solvate, a polymorph, a metabolite, a pharmaceutically acceptable salt, or a prodrug thereof:



G

wherein:

Cy represents a chemical bond, 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl, provided that when the heterocyclyl contains an N atom, the heterocyclyl may be bonded to the carbon atom at the 2-position of the pyrimidine ring in formula G via the N atom or a C atom thereof;

W represents a chemical bond, CH, O, S, N, -S(O)-, -$S(O)_2$-, -C(O), C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene;

R_2 is absent or selected from H and the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d1}: C_{6-20} aryl and 5- to 20-membered heteroaryl;

$R_{2'}$ is absence or represents H, halogen, OH, CN, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d2}: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20}

cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, and NH_2;

provided that R_2 and $R_{2'}$ are not both "absent";

or alternatively, R_2 and $R_{2'}$, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d3}: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and 6- to 20-membered aryl;

R_a represents H or -X-R_3;

X represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_3 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d4}: C_{1-20} alkyl, -$C(O)R_{61}$, -$C(O)OR_{62}$, -$OC(O)R_{63}$, and NH_2;

R_b represents H or -Y-R_4;

Y represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_4 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d5}: C_{1-20} alkyl, -$C(O)R_{61}$, -$C(O)OR_{62}$, -$OC(O)R_{63}$, and NH_2;

provided that R_a and R_b are not both H;

or R_a and R_b, together with the atoms linked thereto, form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d6}: C_{5-20} cycloalkenyl, 3- to 20-membered heterocyclyl, 5- to 20-membered heteroaryl, and 6- to 20-membered aryl;

R_{d1}, R_{d2}, R_{d3}, R_{d4}, R_{d5}, and R_{d6} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, -

$C(O)R_{31}$, $-CH_2-C(O)R_{31}$, $-C(O)OR_{32}$, $-CH_2C(O)OR_{32}$, $-C(O)NHR_{32}$, $-CH2C(O)NHR_{32}$, $-OC(O)R_{33}$, $-S(O)_2R_{34}$, $-S(O)_2OR_{35}$, $-OS(O)_2R_{36}$, and $-P(O)(OR_{37})(OR_{38})$;

or when two or more substituents selected from R_{d1}, R_{d2}, R_{d3}, R_{d4}, R_{d5}, and R_{d6} are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_c are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{31}$, $-C(O)OR_{32}$, $-OC(O)R_{33}$, $-S(O)_2R_{34}$, $-S(O)_2OR_{35}$, $-OS(O)_2R_{36}$, and $-P(O)(OR_{37})(OR_{38})$;

m is selected from integers from 1 to 10;

R_e are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{41}$, $-C(O)OR_{42}$, $-OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

or when two or more substituents selected from R_e are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_f are identical or different, and are each independently selected from H, halogen, OH, CN,

NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{51}$, $-C(O)OR_{52}$, $-OC(O)R_{53}$, $-S(O)_2R_{54}$, $-S(O)_2OR_{55}$, $-OS(O)_2R_{56}$, and $-P(O)(OR_{57})(OR_{58})$;

or when two or more substituents selected from R_f are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_g are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, and R_{58} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

the 3- to 20-membered heterocyclyl represents a saturated or unsaturated non-aromatic ring or ring system; for example, it is a 4-, 5-, 6-, or 7-membered monocyclic ring system, a 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic (e.g., fused, bridged, or spiro) ring system, or a 10-, 11-, 12-, 13-, 14-, or 15-membered tricyclic ring system, and contains at least one, e.g., 1, 2, 3, 4, 5, or more heteroatoms independently selected from O, S, and N, wherein N and S may also be optionally oxidized to various oxidized forms to form nitrogen oxides, -S(O)-, or $-S(O)_2-$;

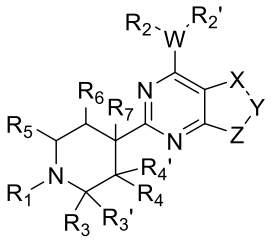
the C_{6-20} aryl represents an aromatic or partially aromatic monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic hydrocarbon ring having 6-20 carbon atoms, which may be a single aromatic ring or multiple aromatic rings fused together;

the 5- to 20-membered heteroaryl represents a monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic aromatic ring system, wherein the aromatic ring system has 5-20

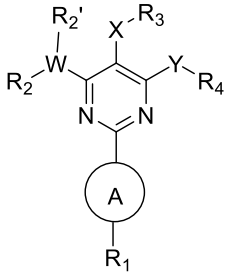
ring atoms and contains 1, 2, 3, 4, 5, or more heteroatoms independently selected from N, O, and S.

According to an embodiment of the present disclosure, the cycloalkyl may be saturated or partially saturated.

According to an embodiment of the present disclosure, the compound represented by formula G, or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof may be selected from compounds represented by the following formulas I, II, III, IV, V, VI, VII, VIII, and IX, or racemates, stereoisomers, tautomers, isotopically labeled compounds, solvates, polymorphs, metabolites, pharmaceutically acceptable salts, or prodrugs thereof:



Formula I



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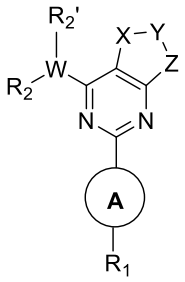

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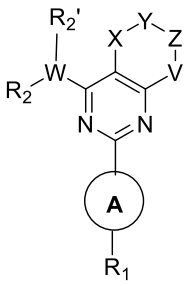

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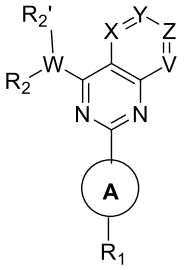
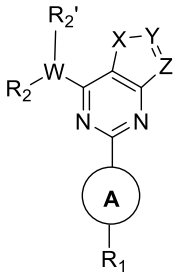
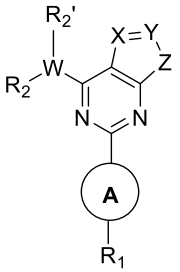


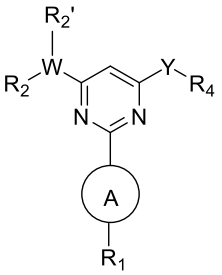
Formula V



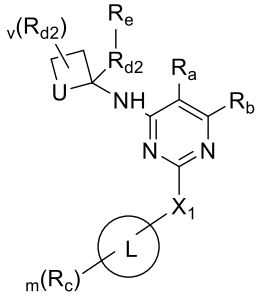
Formula VI



Formula VII



Formula VIII

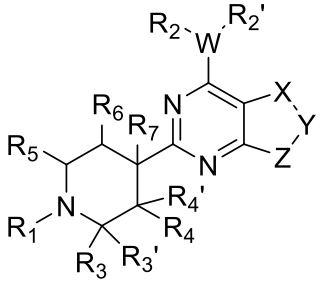


Formula IX

The groups in the above formulas I to IX may independently have the definitions in the context

of the specification of the present disclosure.

According to an embodiment of the present disclosure, the compound of formula I may have the following definitions:



I

wherein:

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic

C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$; or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two,

or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, $CO\text{-}NH_2$, $CO\text{-}NH\text{-}CH_3$, $\text{-}CO\text{-}N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic

ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

R_3 represents H, C_{1-6} alkyl, F, chlorine, bromine, hydroxyl, -CN, $-CH_2CN$, $-CH_2COOR$, -COOR, -CO-$NH(CH_3)C_{1-3}$ fluoroalkyl, (C_{1-6} alkyl)-OH, (C_{1-6} alkyl)-OCH_3, (C_{1-6} alkyl)-NH_2, (C_{1-6} alkyl)-N(C_{1-3} alkyl), or (C_{1-6} alkyl)-NH;

$R_{3'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-20} aryl, C_{6-20} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more groups selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_3 and $R_{3'}$ together represent oxo, methylene, ethylene, and propylene, which may be optionally substituted with substituents selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and O-(C_{1-3} alkyl);

R_4 represents H, C_{1-6} alkyl, F, chlorine, bromine, hydroxyl, -CN, $-CH_2CN$, $-CH_2COOR$, -COOR, -CO-$NH(CH_3)C_{1-3}$ fluoroalkyl, (C_{1-6} alkyl)-OH, (C_{1-6} alkyl)-OCH_3, (C_{1-6} alkyl)-NH_2, (C_{1-6} alkyl)-N(C_{1-3} alkyl), or (C_{1-6} alkyl)-NH;

$R_{4'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-20} aryl, C_{6-20} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more groups selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_4 and $R_{4'}$ together represent oxo, methylene, ethylene, and propylene, which may be optionally substituted with substituents selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and O-(C_{1-3} alkyl);

R_5 and R_6 independently represent H, F, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-6} alkyl-OH, C_{1-6} alkenyl-OCH_3, C_{1-6} alkyl-NH_2, C_{1-6} alkynyl-NH(C_{1-3} alkyl), and C_{1-6} alkyl-N(C_{1-3} alkyl)$_2$;

or R_1 and R_3, together with the C- and N-atoms of piperidine, form a saturated or partially saturated 5- or 7-membered heterocyclic group that contains two or three nitrogen atoms, which may be optionally substituted with groups selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

or R_3 and R_6 together form a bridged ring of methylene, ethylene, and propylene, which may be optionally substituted with groups selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

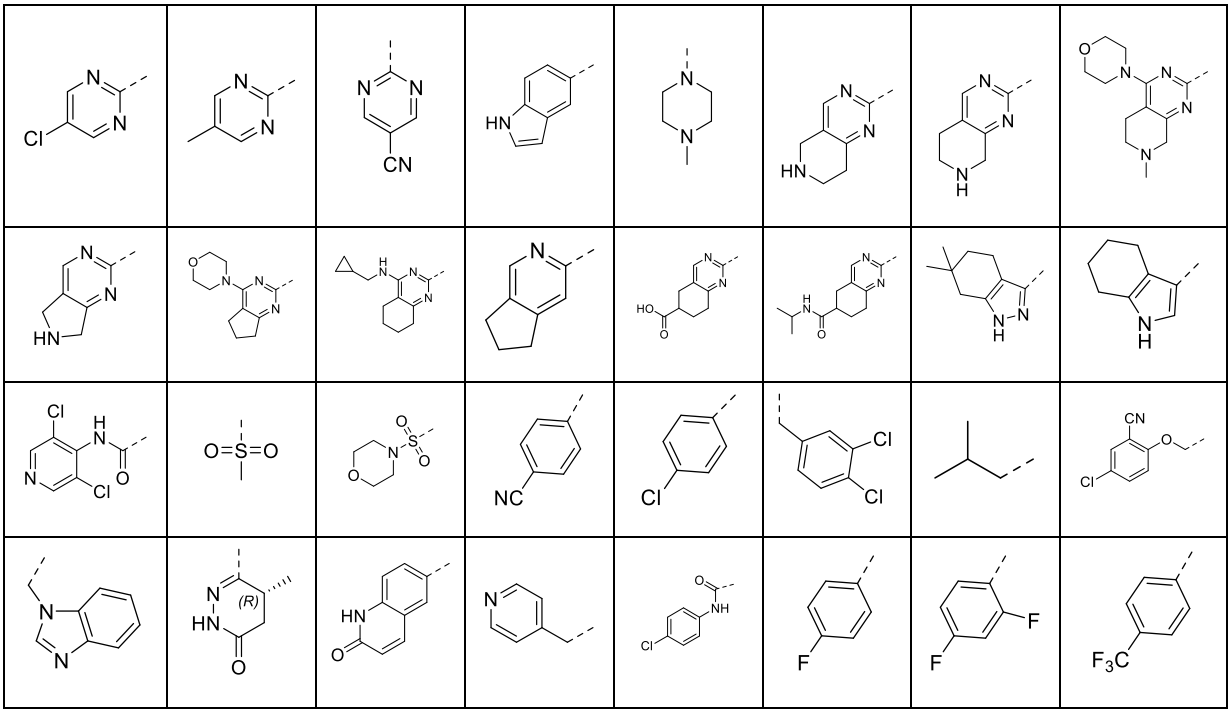
or R_3 and R_5 together form a bridged ring of methylene, ethylene, and propylene, which may be optionally substituted with groups selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

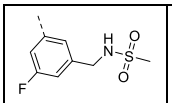
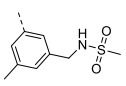
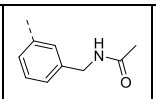
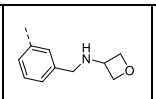
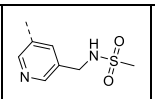
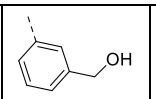
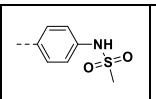
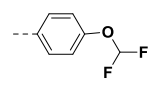
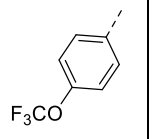
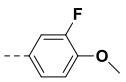
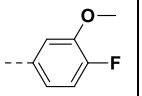
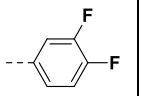
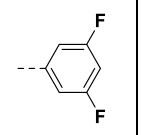
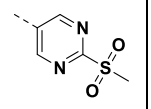
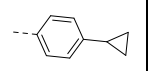
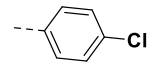
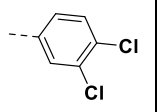
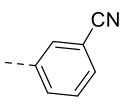
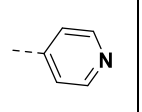
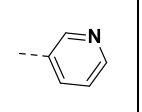
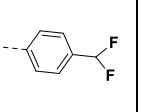
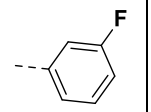
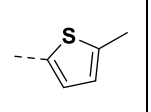
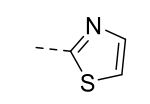
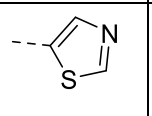
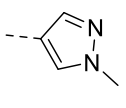
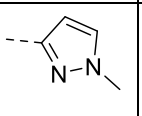
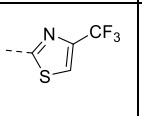
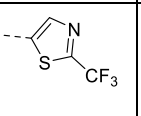
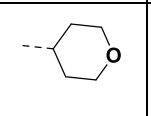
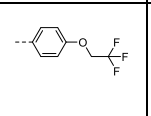
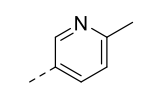
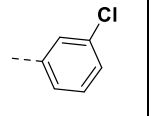
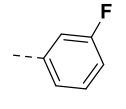
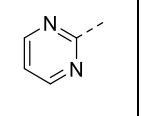
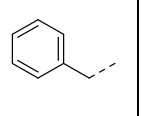
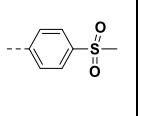
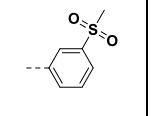
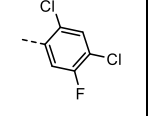
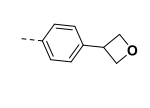
or R_3 and R_4 together form a bridged ring of methylene, ethylene, and propylene, which may be optionally substituted with groups selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

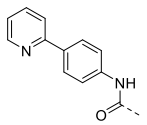
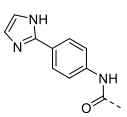
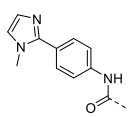
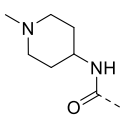
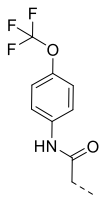
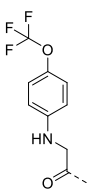
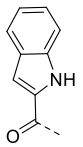
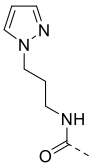
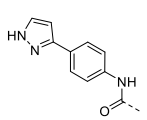
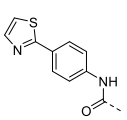
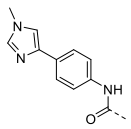
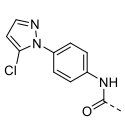
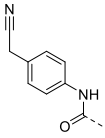
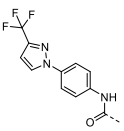
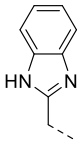
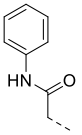
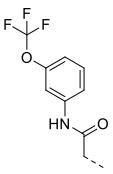
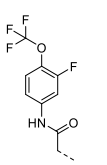
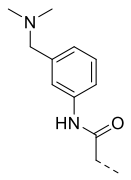
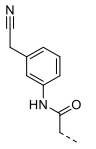
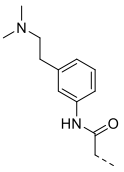
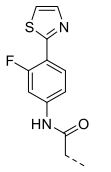
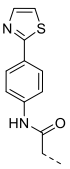
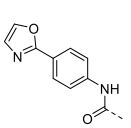
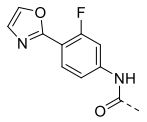
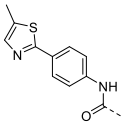
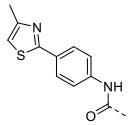
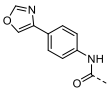
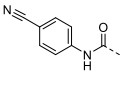
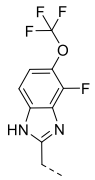
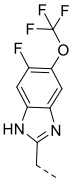
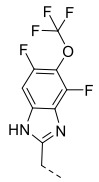
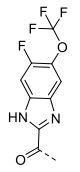
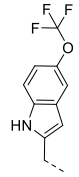
or R_4 and R_6 together form a bridged ring of methylene, ethylene, and propylene, which may be optionally substituted with groups selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

or R_4 and R_7, together with the carbon atom linked thereto, form a double bond.

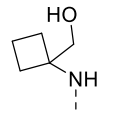
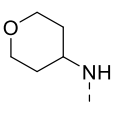
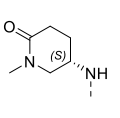
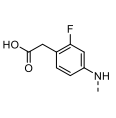
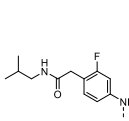
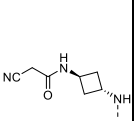
According to an embodiment of the present disclosure, examples of R_1 may be selected from the following groups:

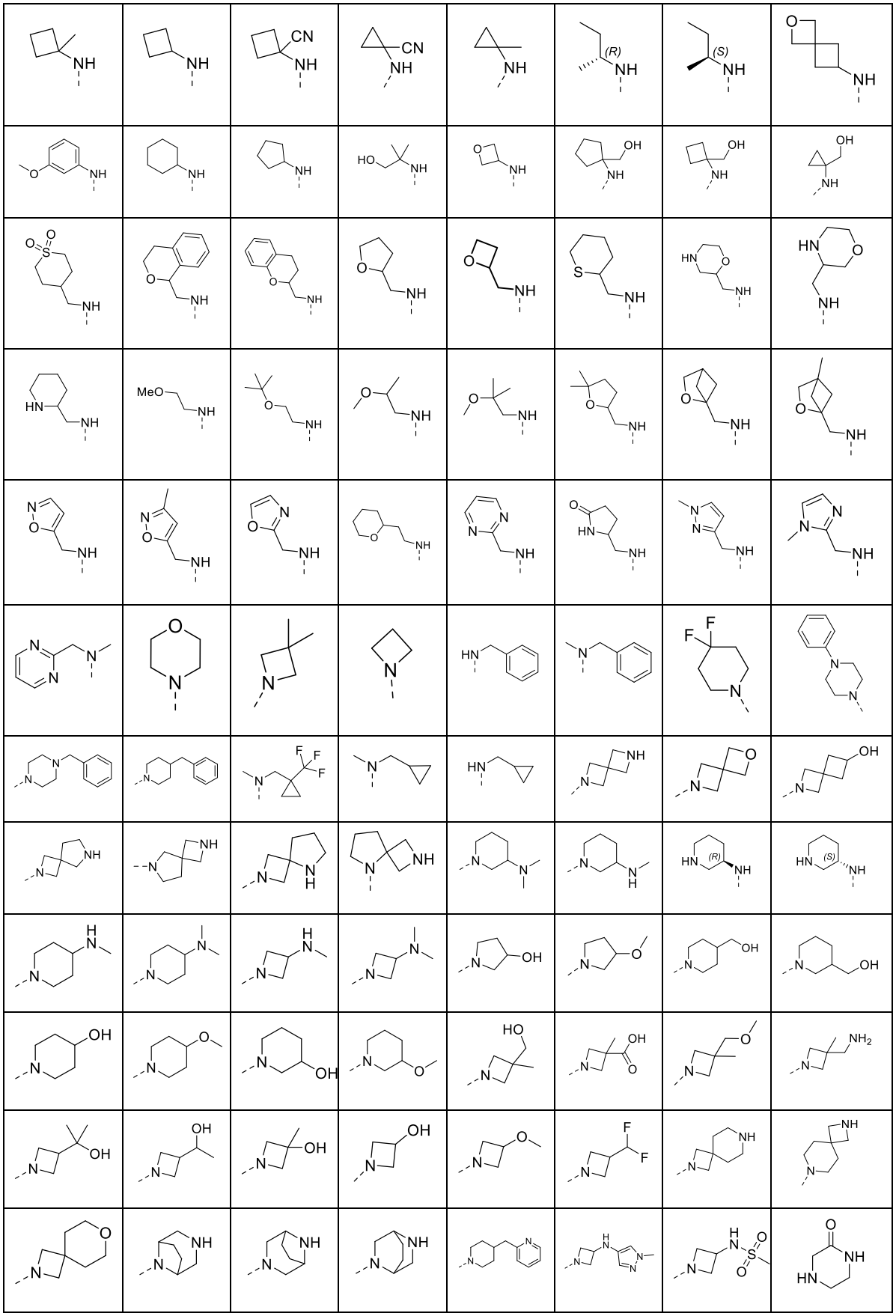


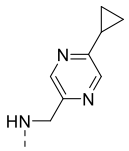
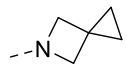
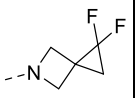
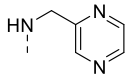
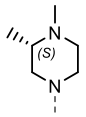
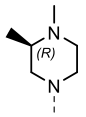
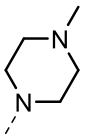
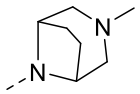
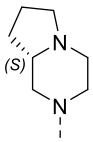
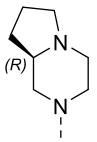
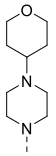
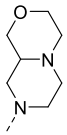
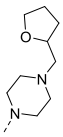
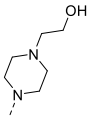
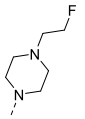
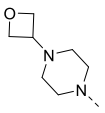
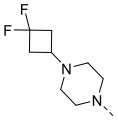
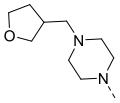
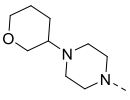
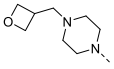
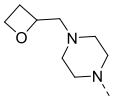
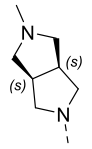
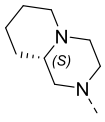
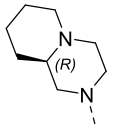
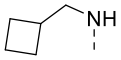
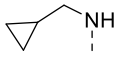
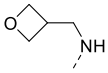
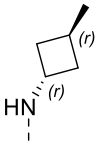
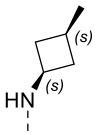
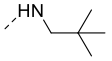
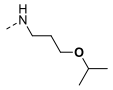
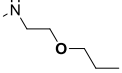
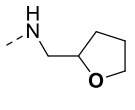
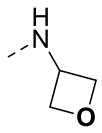
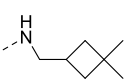
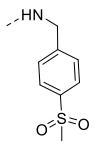
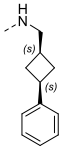
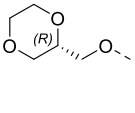
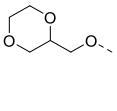
							
							
							
							
							

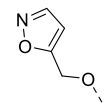
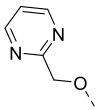
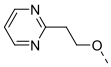
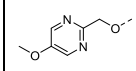
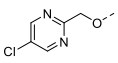
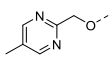
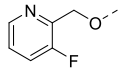
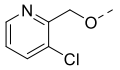
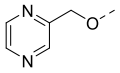
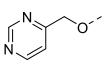
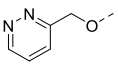
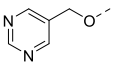
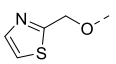
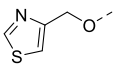
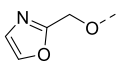
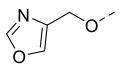
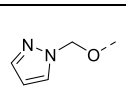
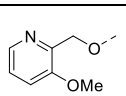
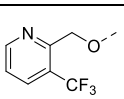
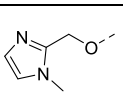
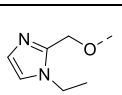
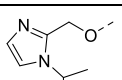
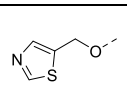
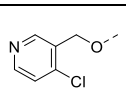
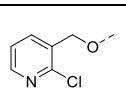
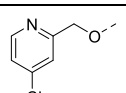
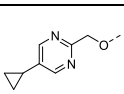
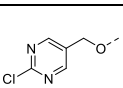
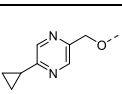
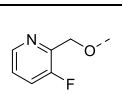
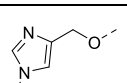
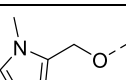
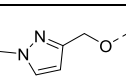
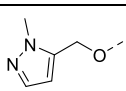
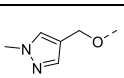
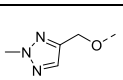
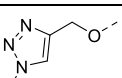
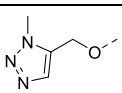
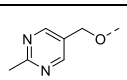
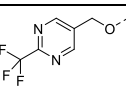
							
							
							
							
							

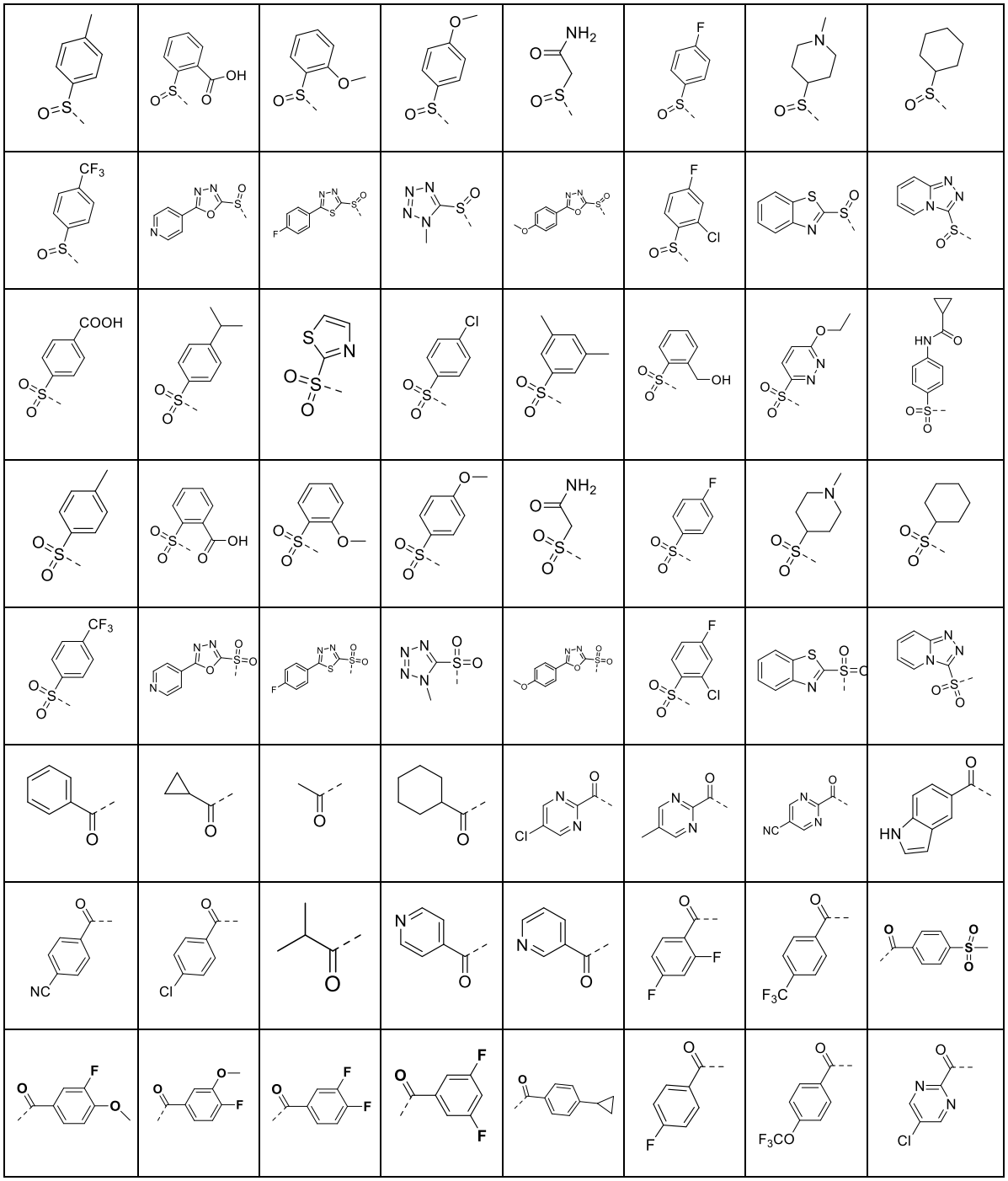
According to an embodiment of the present disclosure, examples of -W-R_2R_2, may be selected from the following groups:

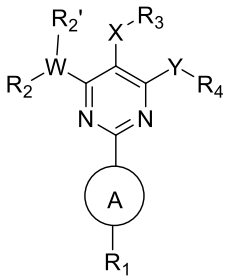




According to an embodiment of the present disclosure, the compound of formula II has the following definitions:



II

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), $C_{1\text{-}2}$ alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, $SO\text{-}R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl,

3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{5-10} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents is optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;
the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{5-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-20} aryl, C_{6-20} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or,

R_2 and $R_{2'}$ together form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

R_3 represents a group selected from aryl and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or independently and optionally substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3,

CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{2.3}$;

R_4 represents a group selected from aryl and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or independently and optionally substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered

heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

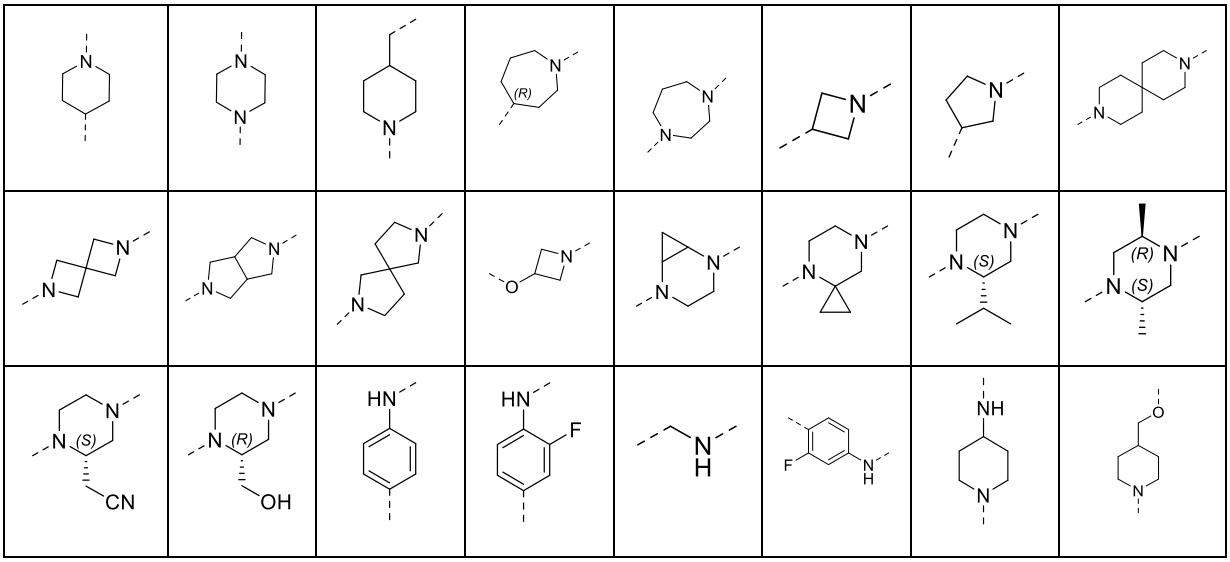
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

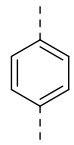
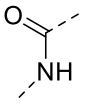
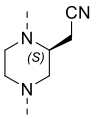
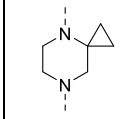
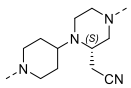
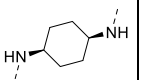
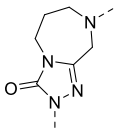
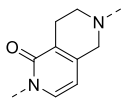
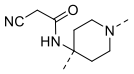
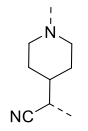
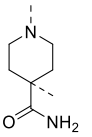
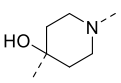
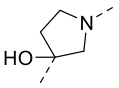
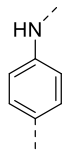
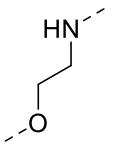
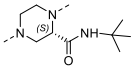
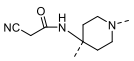
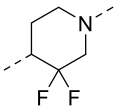
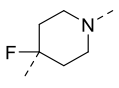
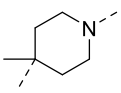
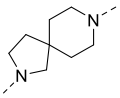
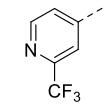
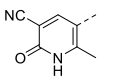
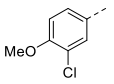
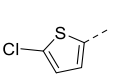
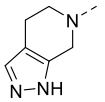
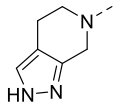
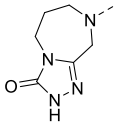
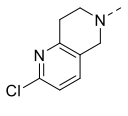
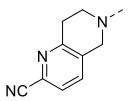
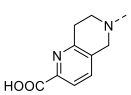
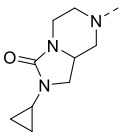
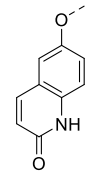
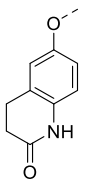
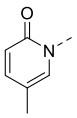
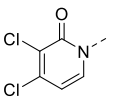
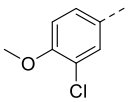
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

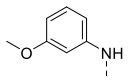
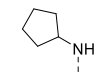
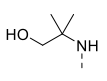
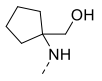
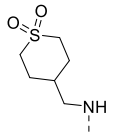
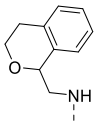
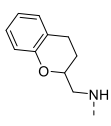
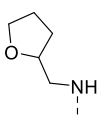
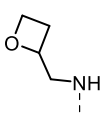
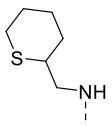
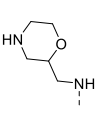
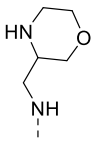
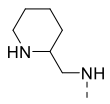
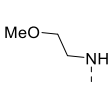
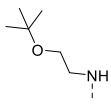
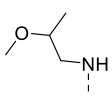
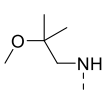
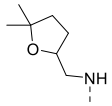
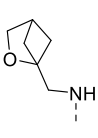
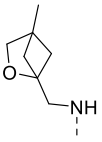
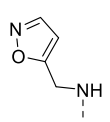
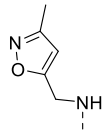
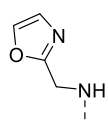
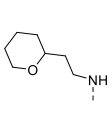
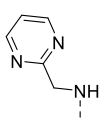
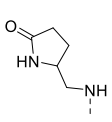
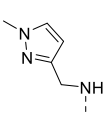
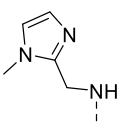
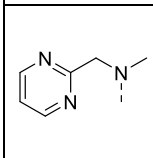
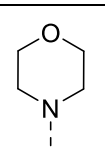
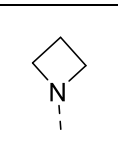
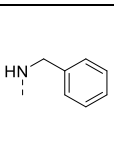
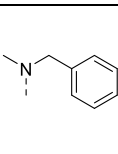
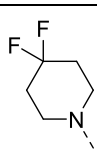
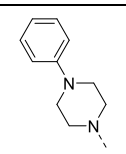
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$.

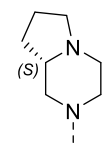
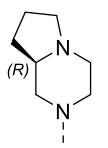
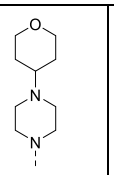
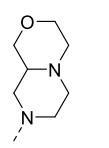
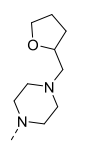
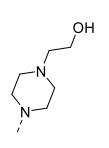
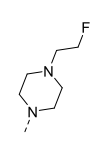
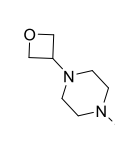
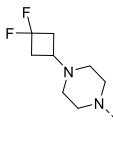
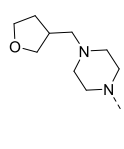
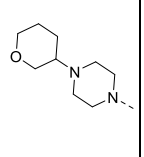
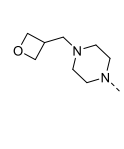
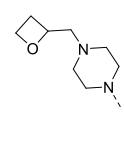
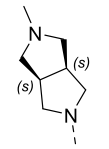
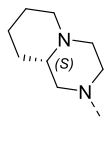
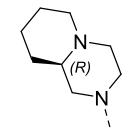
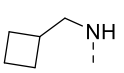
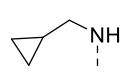
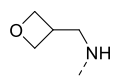
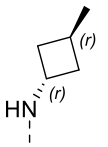
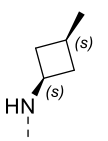
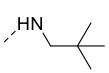
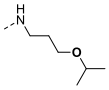
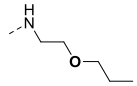
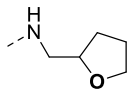
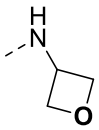
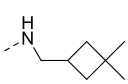
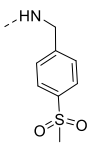
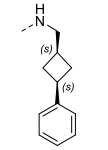
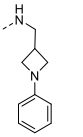
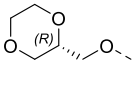
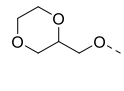
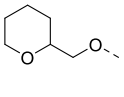
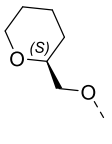
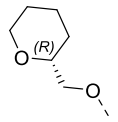
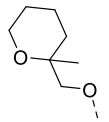
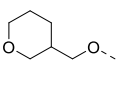
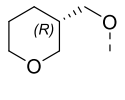
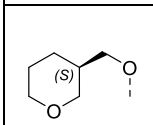
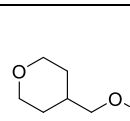
According to an embodiment of the present disclosure, examples of ring A may be selected from the following groups:

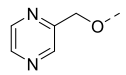
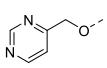
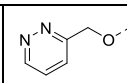
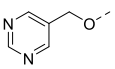
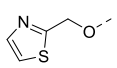
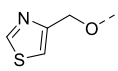
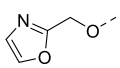
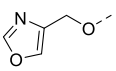
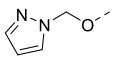
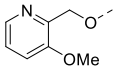
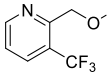
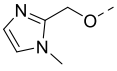
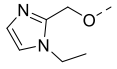
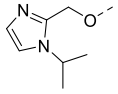
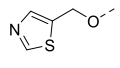
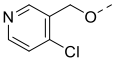
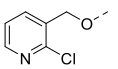
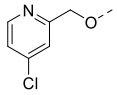
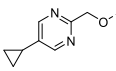
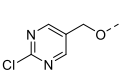
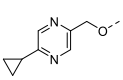
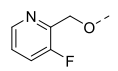
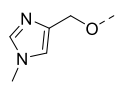
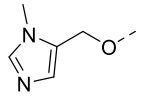
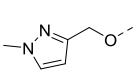
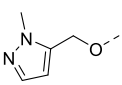
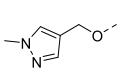
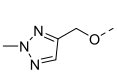
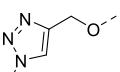
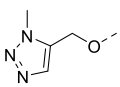
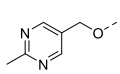
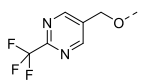
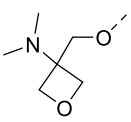
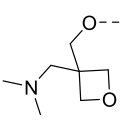
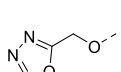
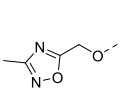
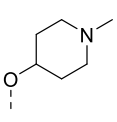
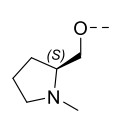
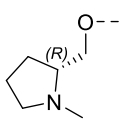
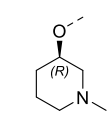


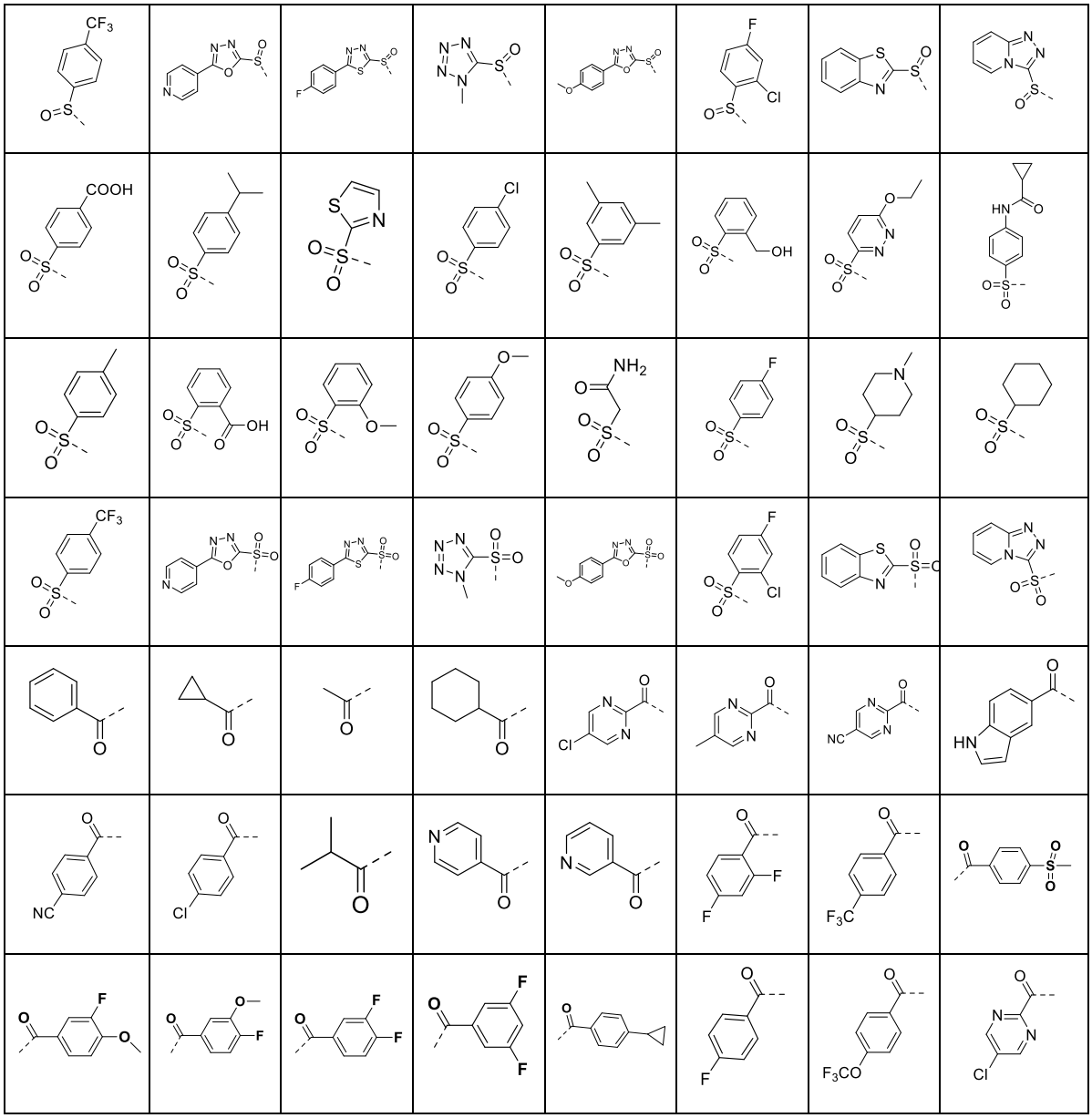
							
							
							
							
							

According to an embodiment of the present disclosure, examples of -W-R_2R_2, may be selected from the following groups:

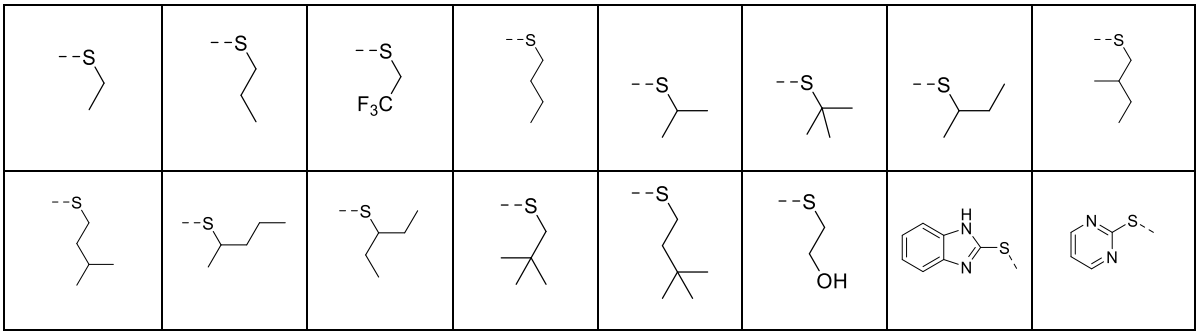
							
							
							
							
							

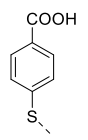
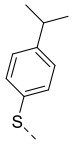
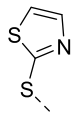
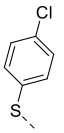
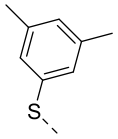
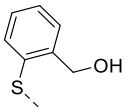
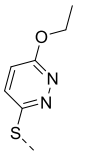
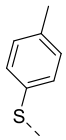
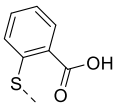
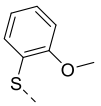
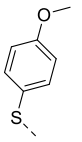
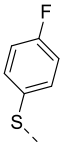
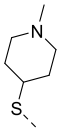
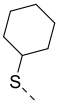
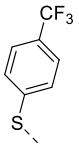
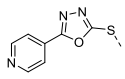
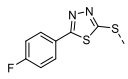
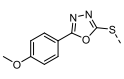
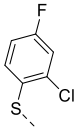
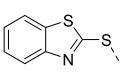
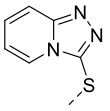
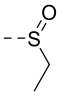
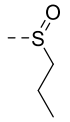
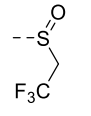
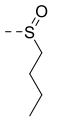
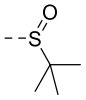
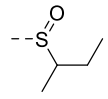
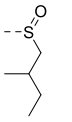
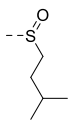
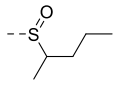
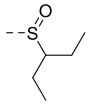
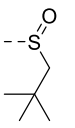
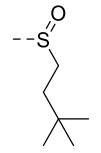
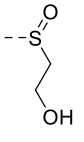
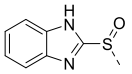
							
							
							
							
							
							

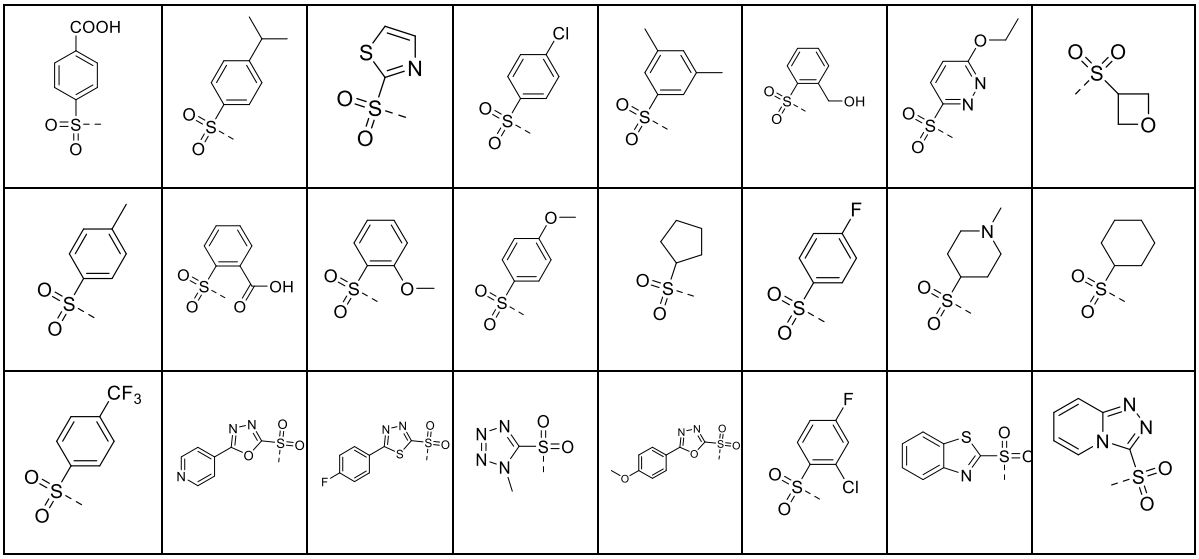
							
							
							
							
							



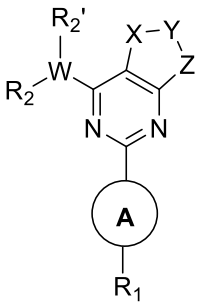
According to an embodiment of the present disclosure, examples of the substituent -X-R_3 may be selected from the following groups:





According to an embodiment of the present disclosure, the compound of formula III has the following definitions:



III

wherein:

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and

optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-N$(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted

with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $NR^{2.2}R^{2.3}$, $CH_2\text{-}NR^{2.2}R^{2.3}$, $CH_2CH_2\text{-}NR^{2.2}R^{2.3}$, $C_{3\text{-}10}$ cycloalkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ fluoroalkyl, CF_3, CHF_2, CH_2F, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}3}$ alkyl-$SOR^{2.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{2.1}$, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, $SR^{2.1}$, $C_{1\text{-}3}$ alkyl-$SR^{2.1}$, SO-$R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SOR^{2.1}$, $SO_2\text{-}R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered, monocyclic or bicyclic, optionally related, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl alcohol, $C_{1\text{-}3}$ haloalkyl, a mono- or bicyclic ring, -$C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-($C_{1\text{-}3}$ alkyl), halogen, $C_{1\text{-}10}$ alkyl, and $C_{6\text{-}20}$ aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from $C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, mono-

or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently

and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

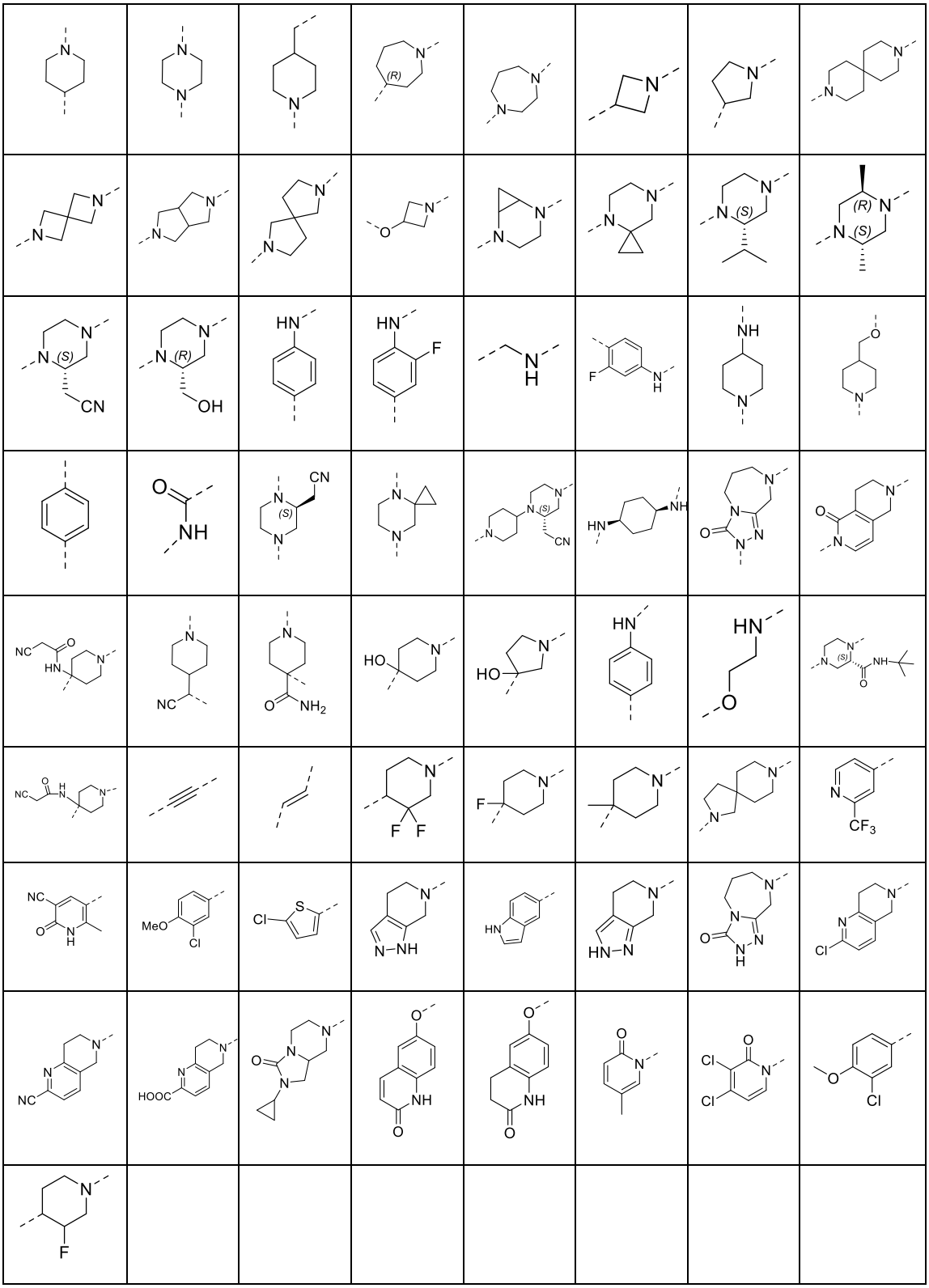
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

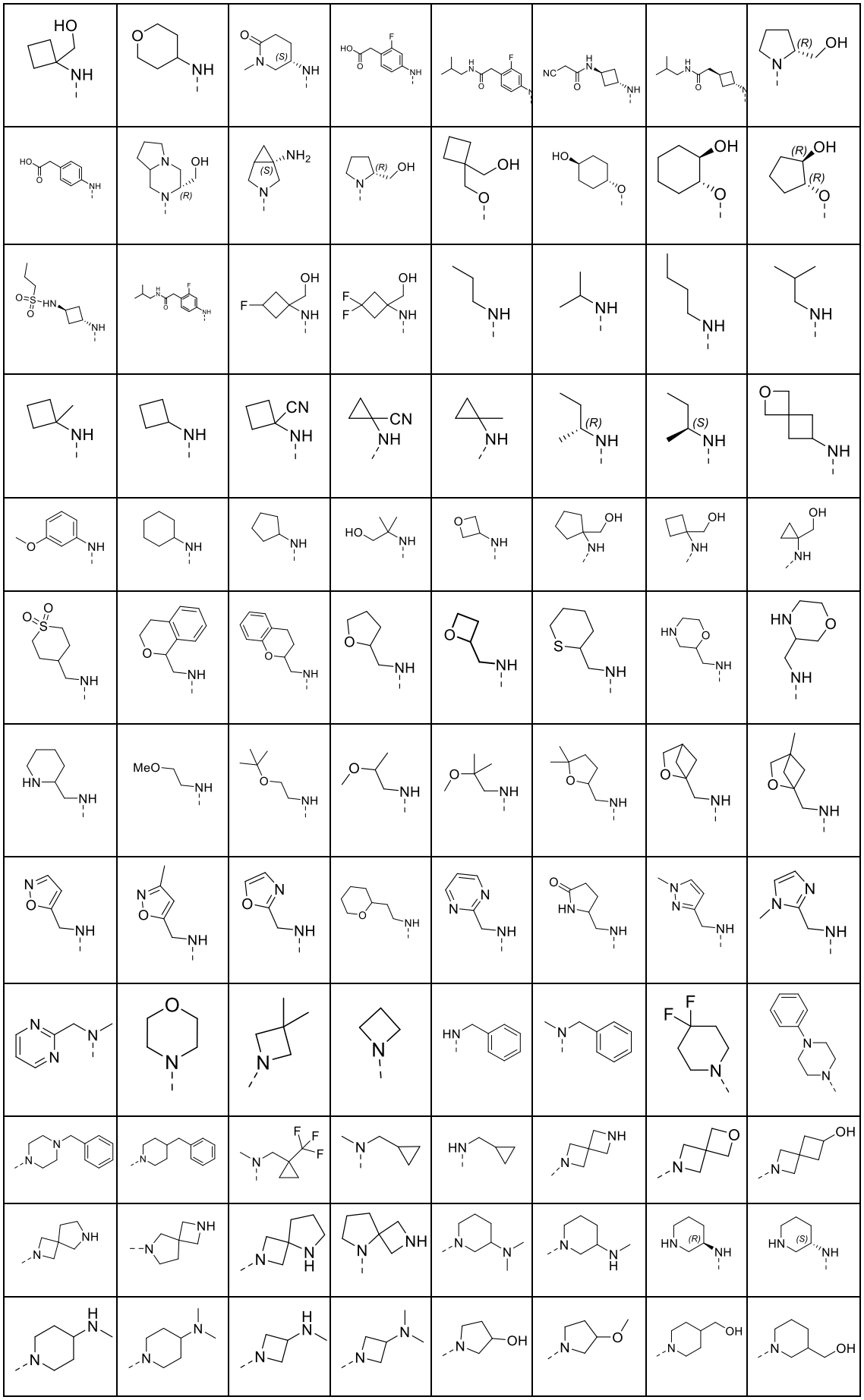
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$.

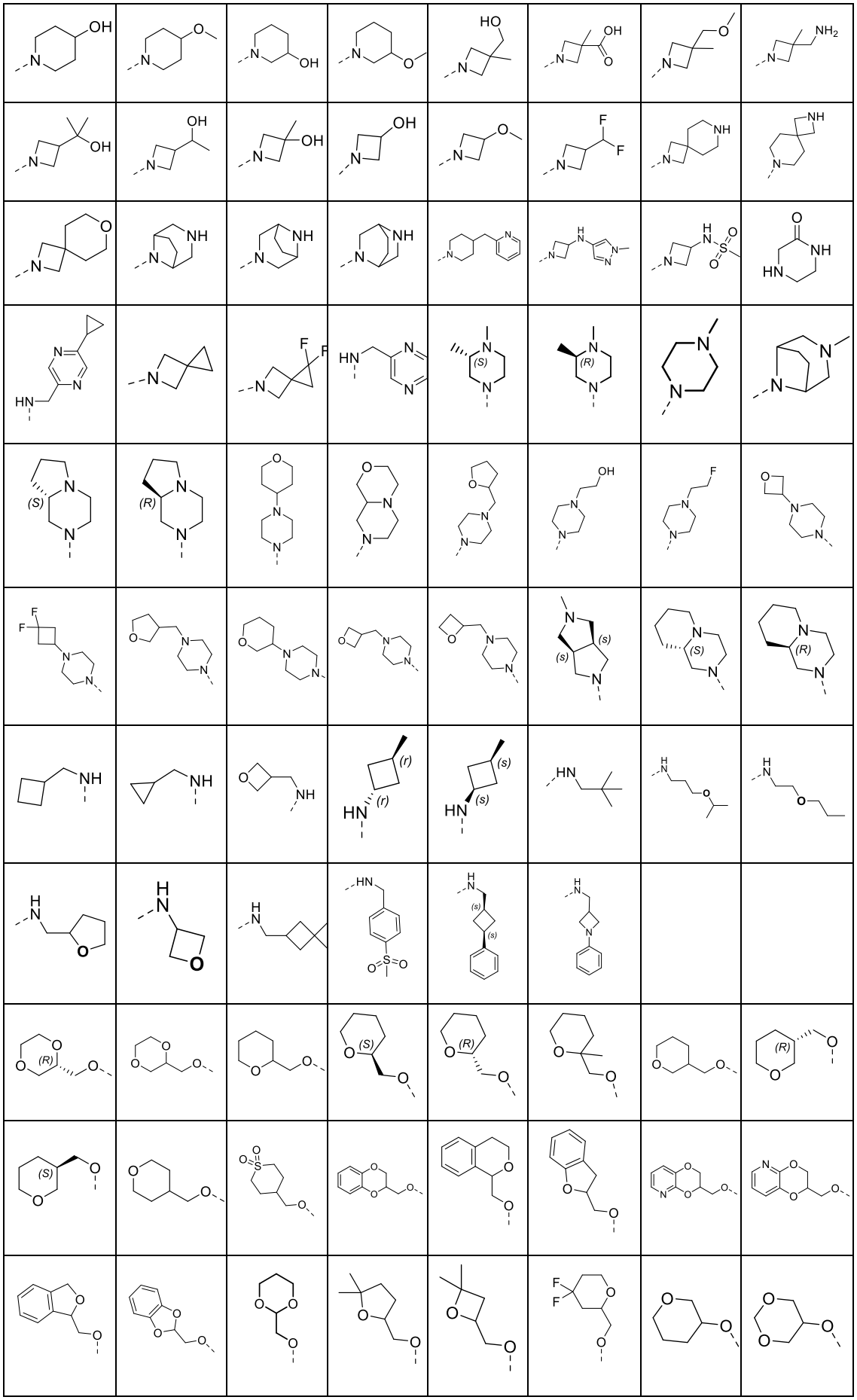
Or, according to an embodiment of the present disclosure,

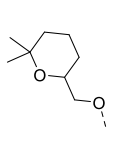
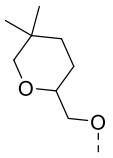
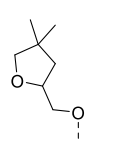
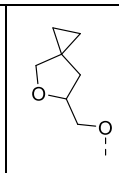
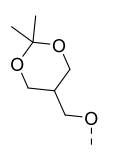
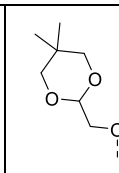
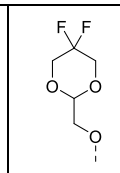
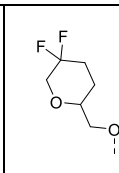
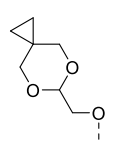
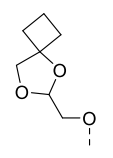
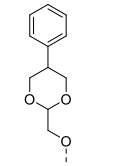
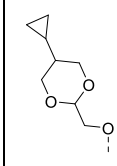
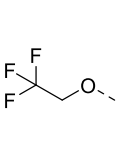
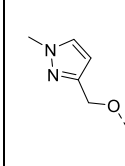
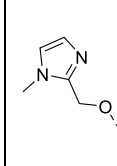
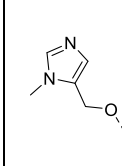
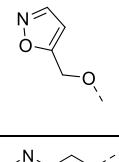
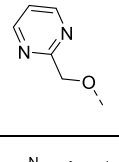
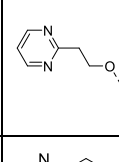
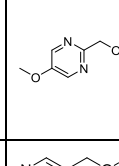
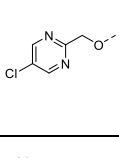
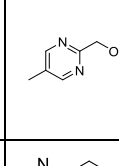
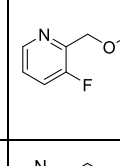
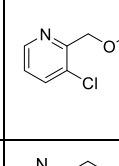
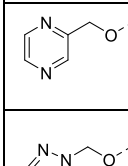
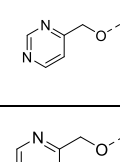
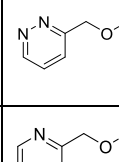
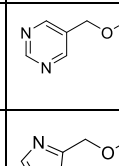
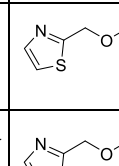
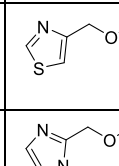
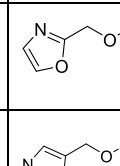
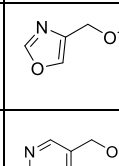
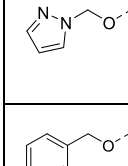
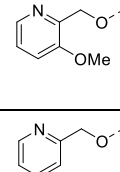
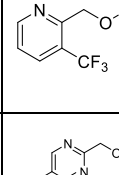
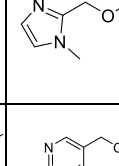
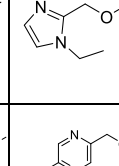
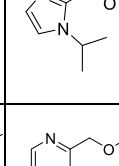
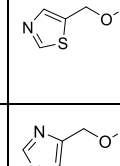
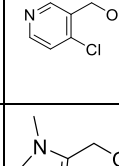
According to an embodiment of the present disclosure, examples of ring A may be selected from the following groups:

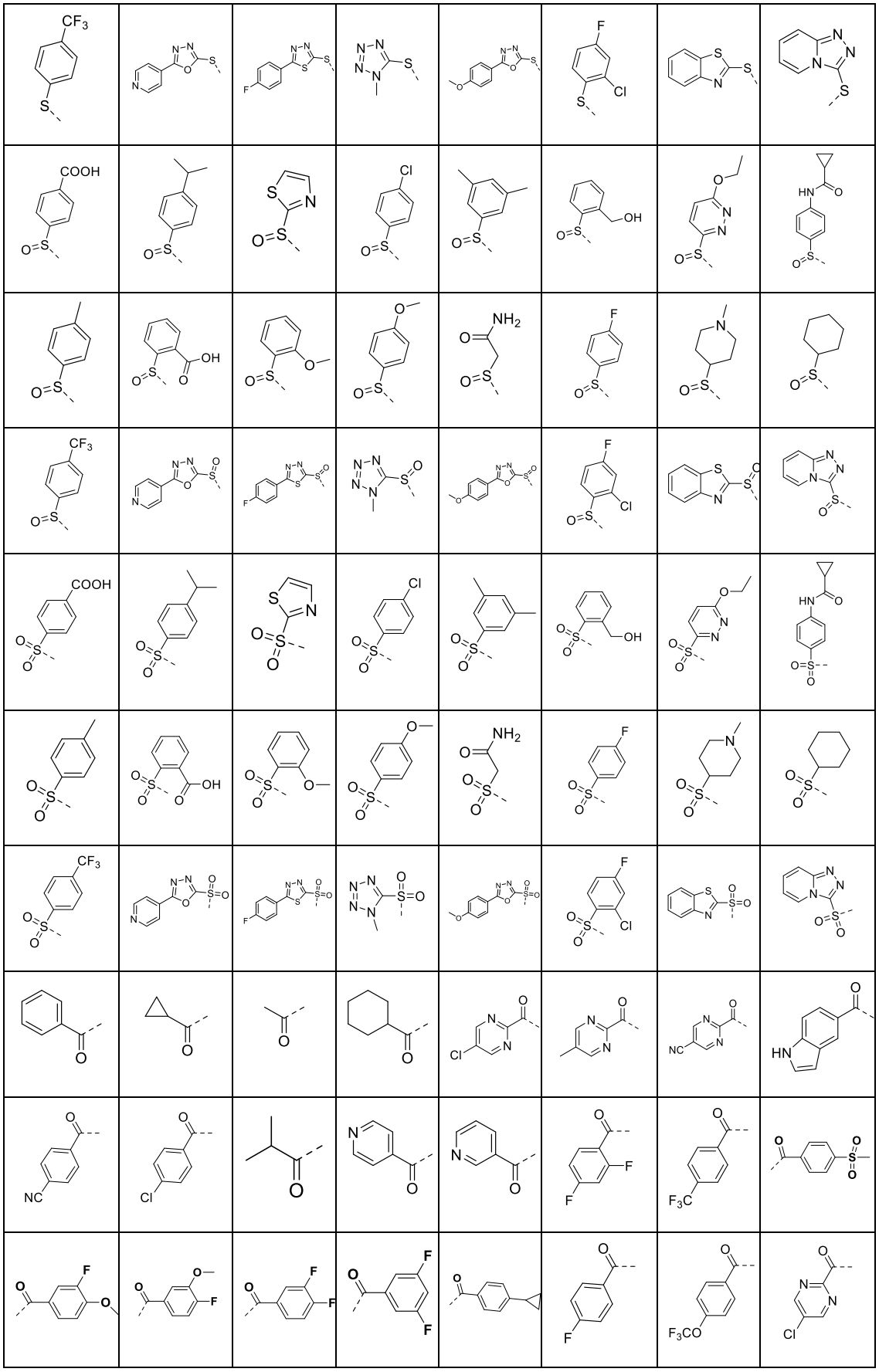


According to an embodiment of the present disclosure, examples of -W-R_2R_2, may be selected from the following groups:



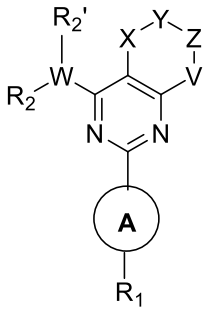




According to an embodiment of the present disclosure, the compound of formula IV has the

following definitions:



IV

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

V represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

or R1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, $SO\text{-}R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring,

5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, $CO\text{-}NH_2$, $CO\text{-}NH\text{-}CH_3$, $\text{-}CO\text{-}N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more

substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CH$CO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein

the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or

partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

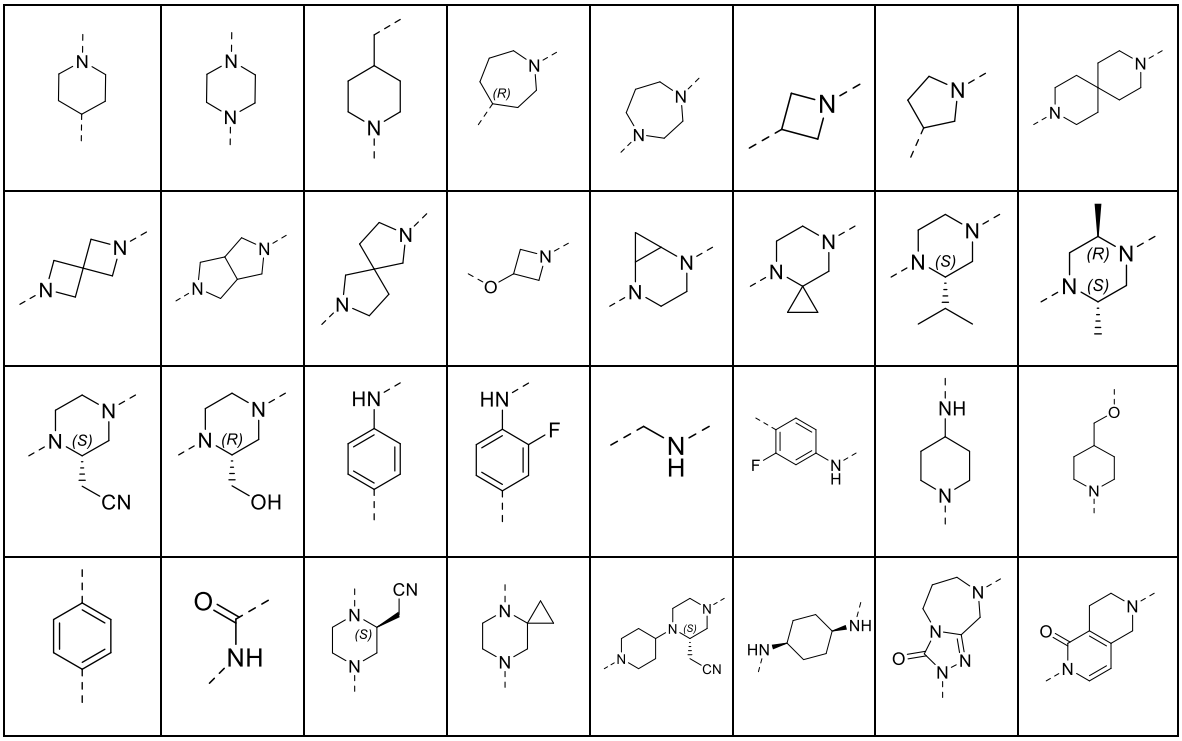
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

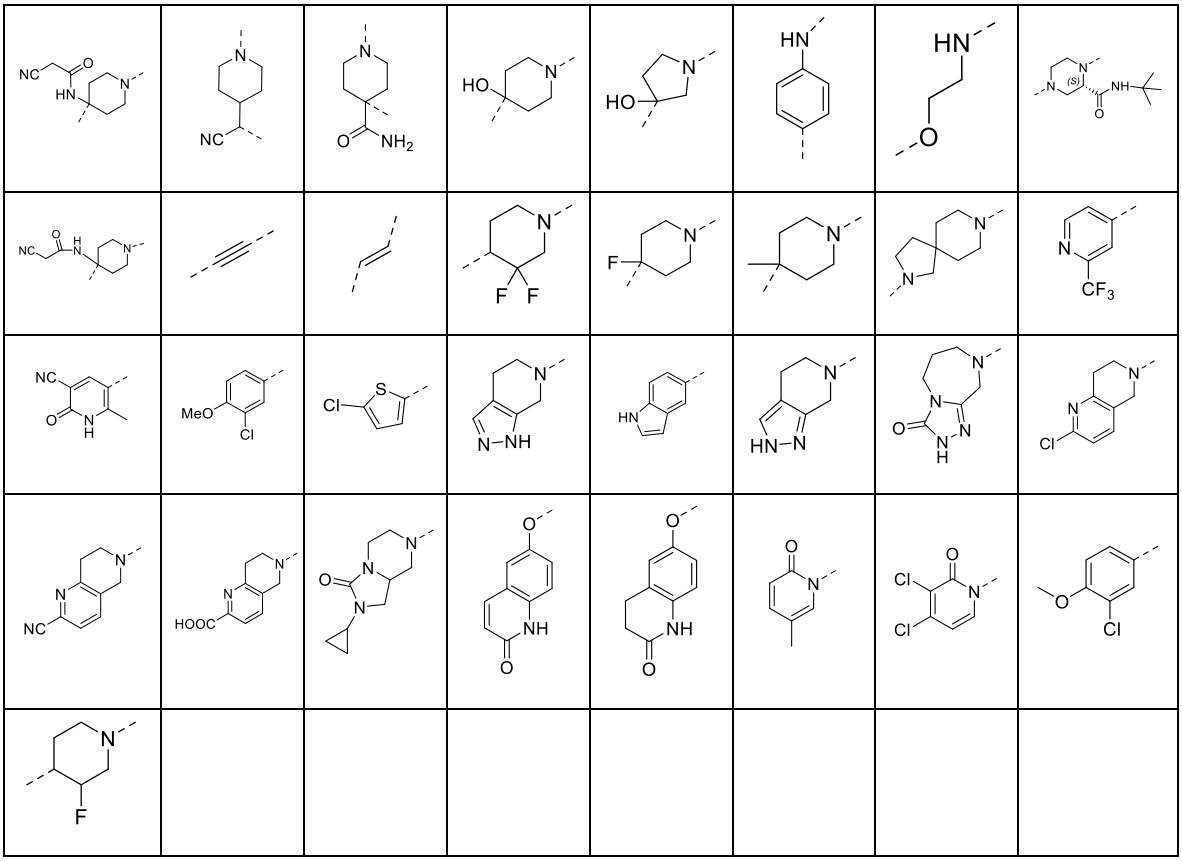
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

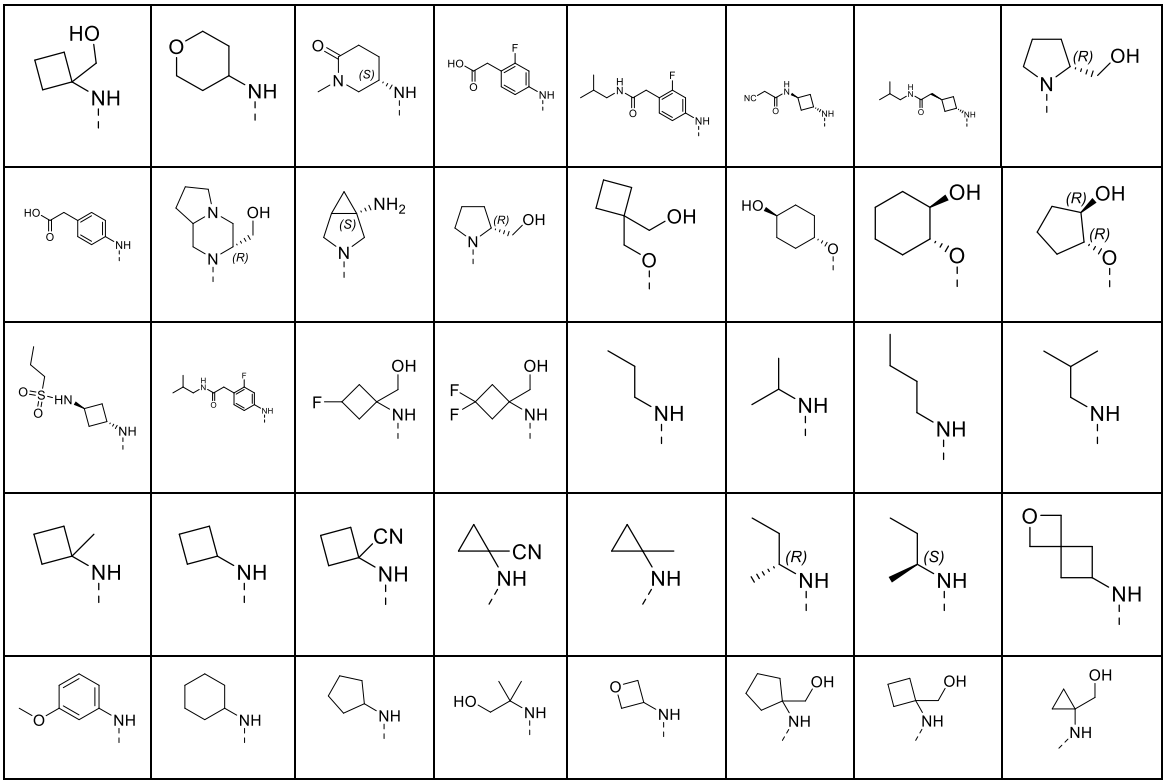
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$.

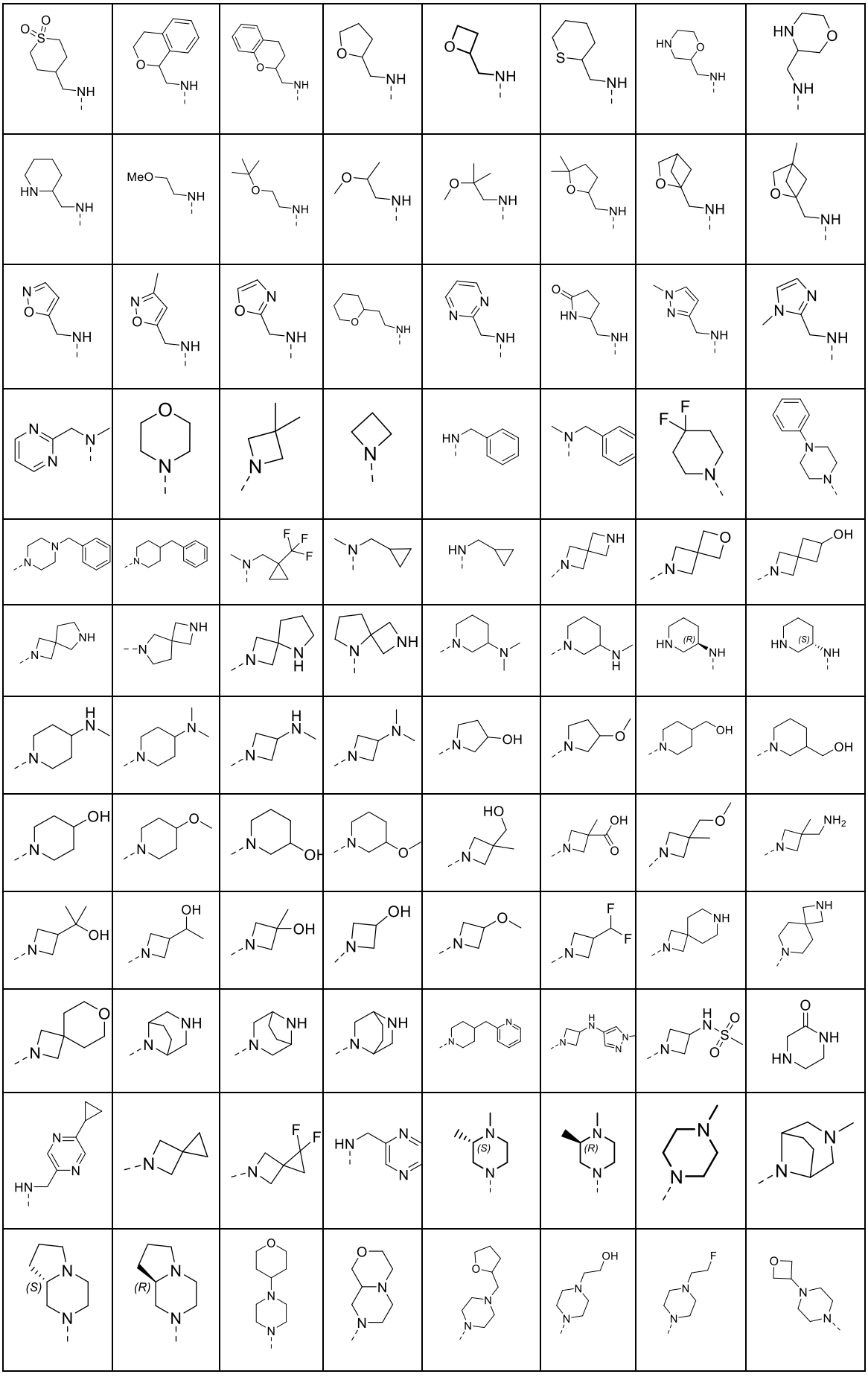
According to an embodiment of the present disclosure, examples of ring A may be selected from the following groups:

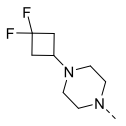
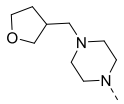
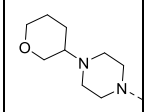
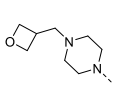
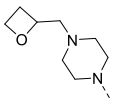
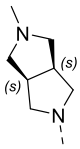
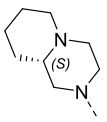
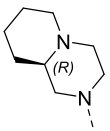
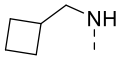
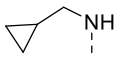
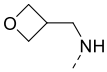
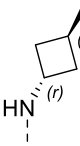
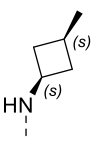
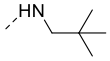
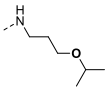
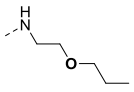
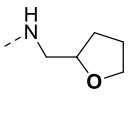
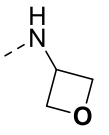
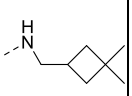
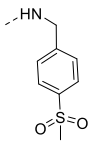
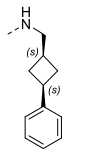
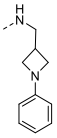
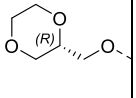
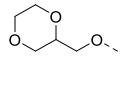
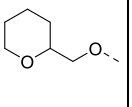
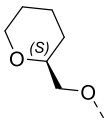
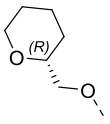
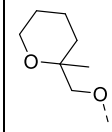
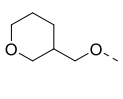
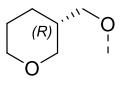
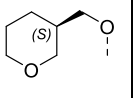
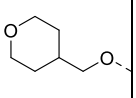
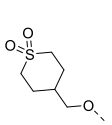
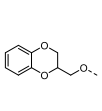
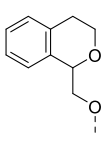
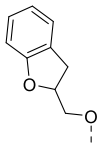
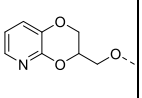
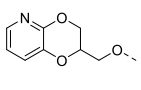
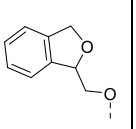
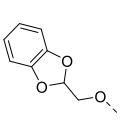


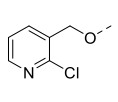
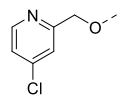
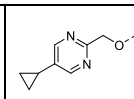
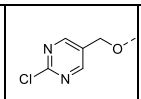
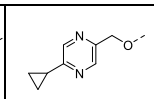
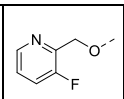
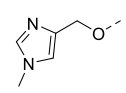
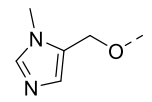
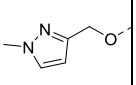
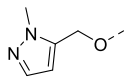
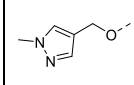
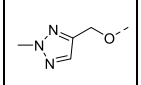
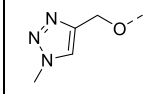
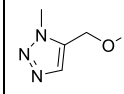
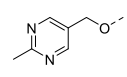
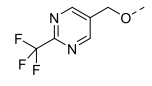
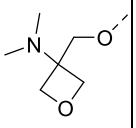
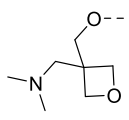
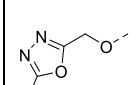
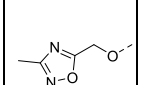
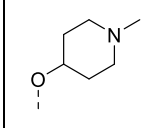
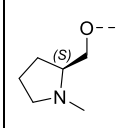
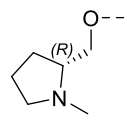
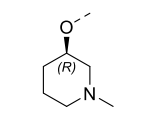
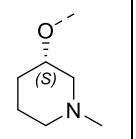
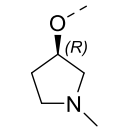
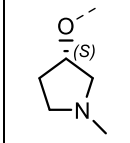
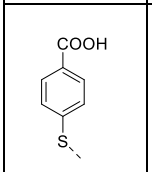
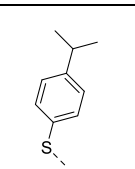
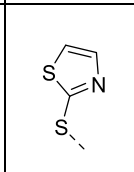
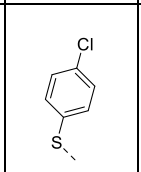
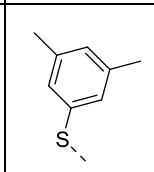
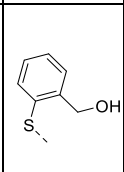
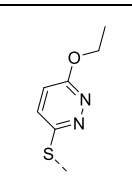
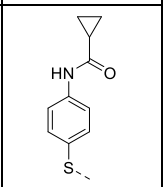
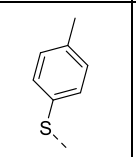
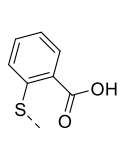
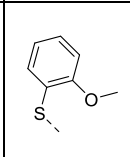
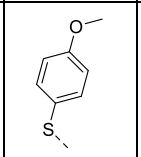
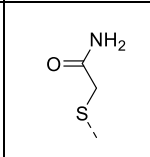


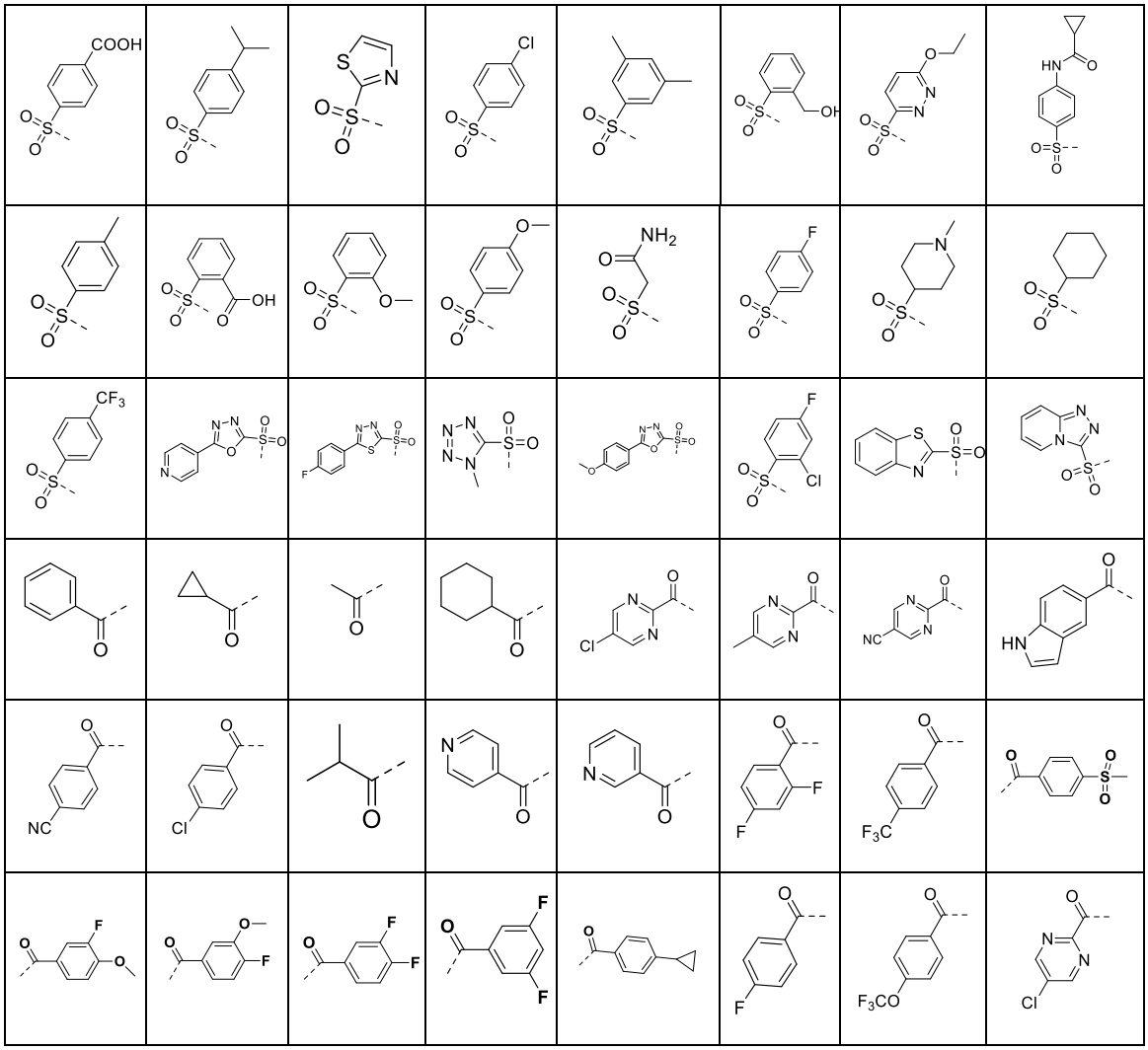
According to an embodiment of the present disclosure, examples of -W-R_2R_2, may be selected from the following groups:



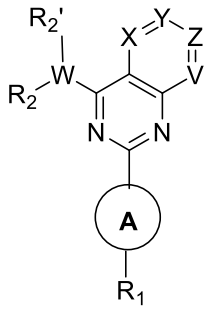




According to an embodiment of the present disclosure, the compound of formula V has the following definitions:



V

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), $C_{1\text{-}2}$ alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

V represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

or,

R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, $SO\text{-}R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

wherein $R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20}

aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$; or,

R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4

heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

wherein $R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or,

R_2 and $R_{2'}$ together form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and

optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

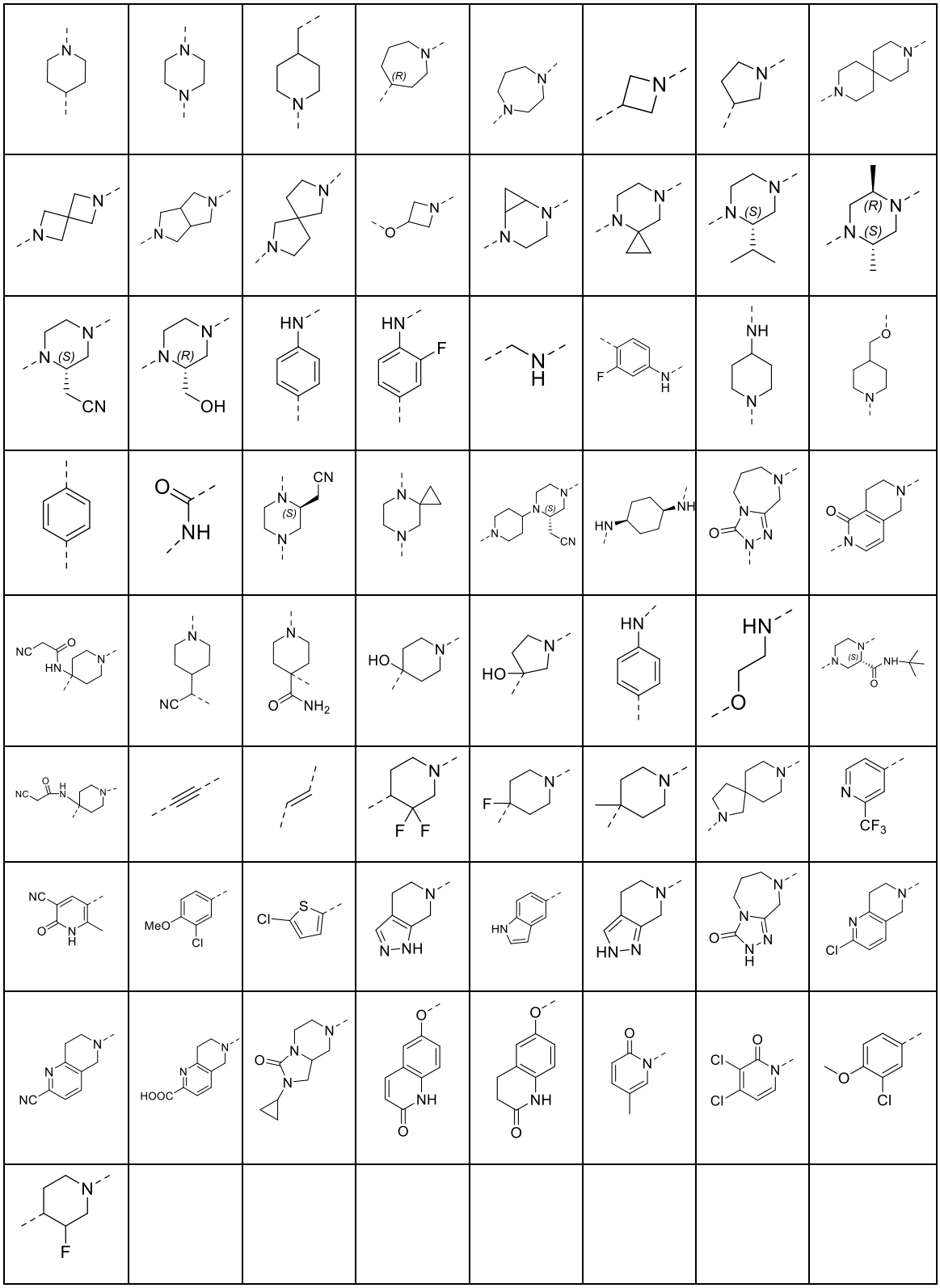
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

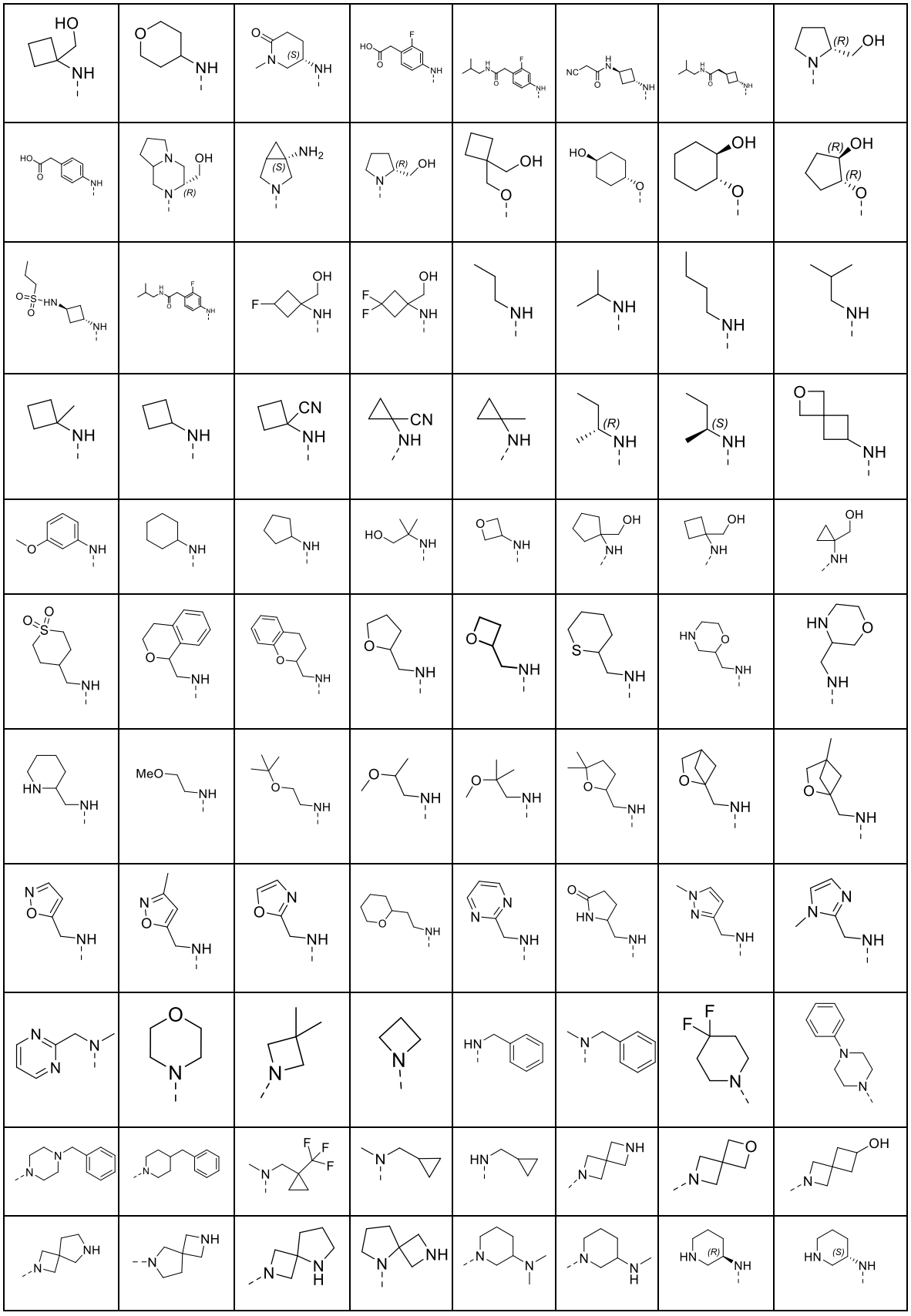
$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

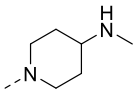
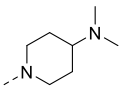
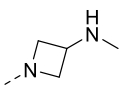
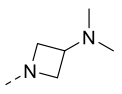
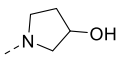
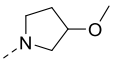
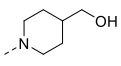
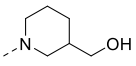
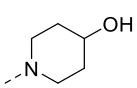
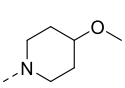
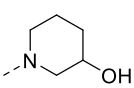
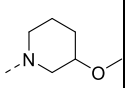
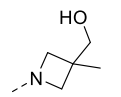
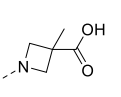
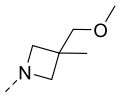
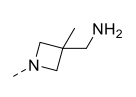
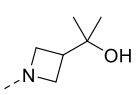
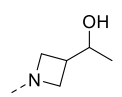
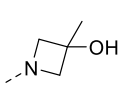
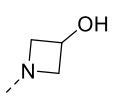
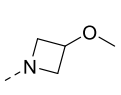
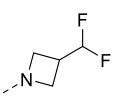
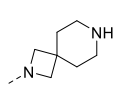
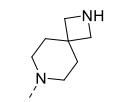
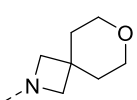
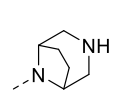
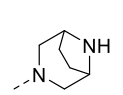
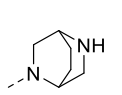
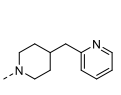
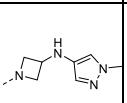
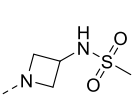
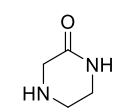
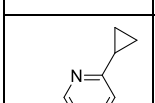
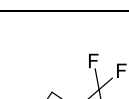
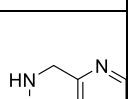
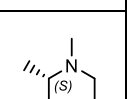
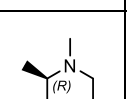
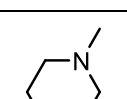
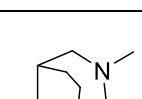
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$.

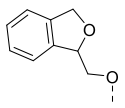
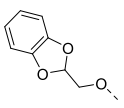
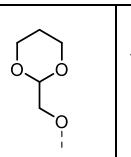
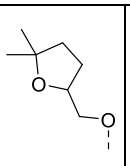
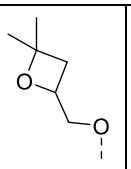
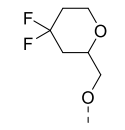
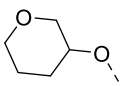
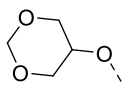
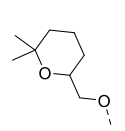
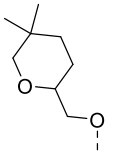
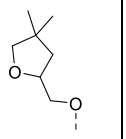
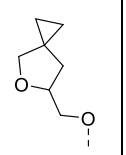
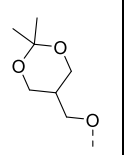
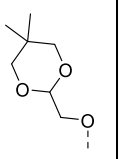
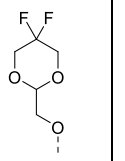
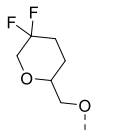
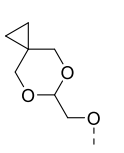
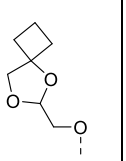
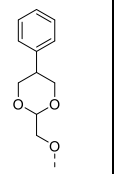
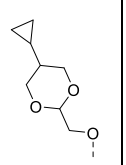
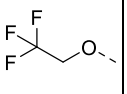
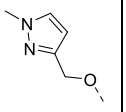
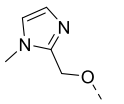
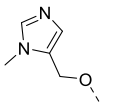
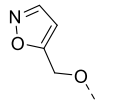
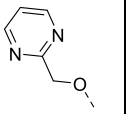
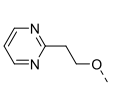
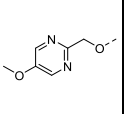
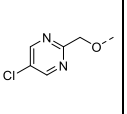
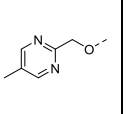
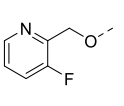
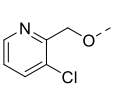
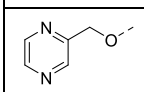
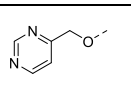
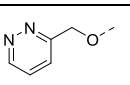
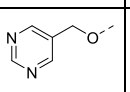
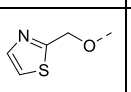
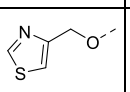
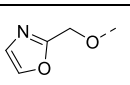
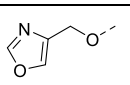
According to an embodiment of the present disclosure, examples of ring A may be selected from the following groups:

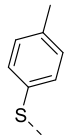
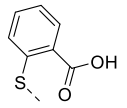
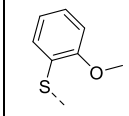
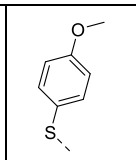
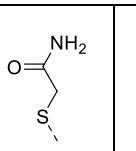
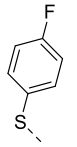
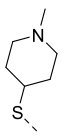
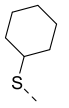
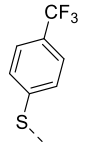
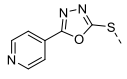
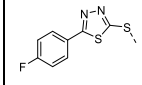
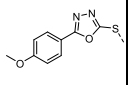
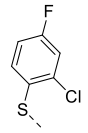
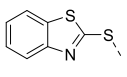
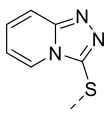
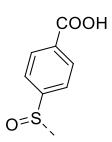
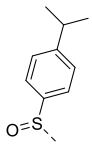
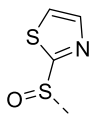
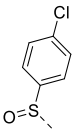
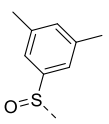
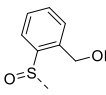
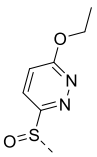
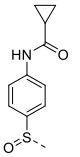
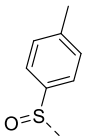
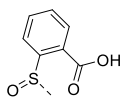
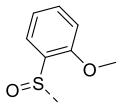
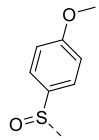
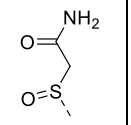
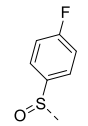
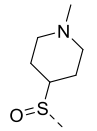
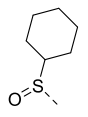
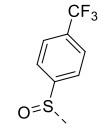
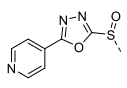
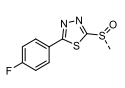
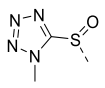
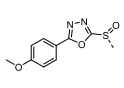
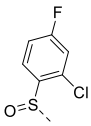
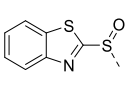
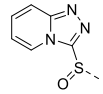


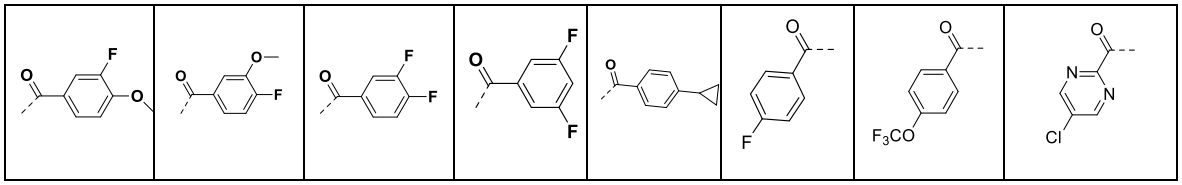
According to an embodiment of the present disclosure, examples of the substituent -W-R_2R_2, may be selected from the following groups:



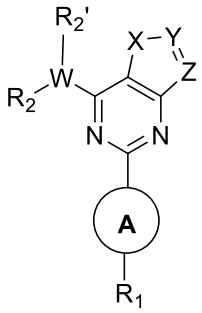
							
							
							
							
							



According to an embodiment of the present disclosure, the compound of formula VI has the following definitions:



VI

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

or,

R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-

$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the

substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$; or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-N$(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$;

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H

and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-

membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

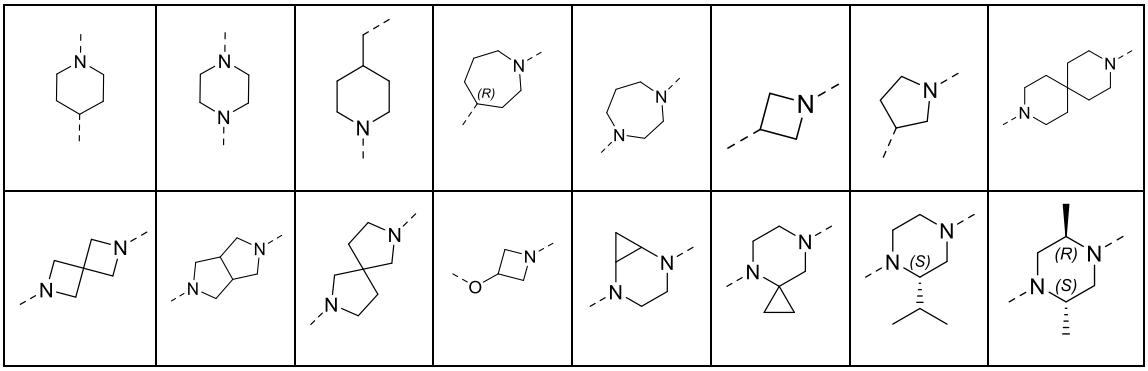
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

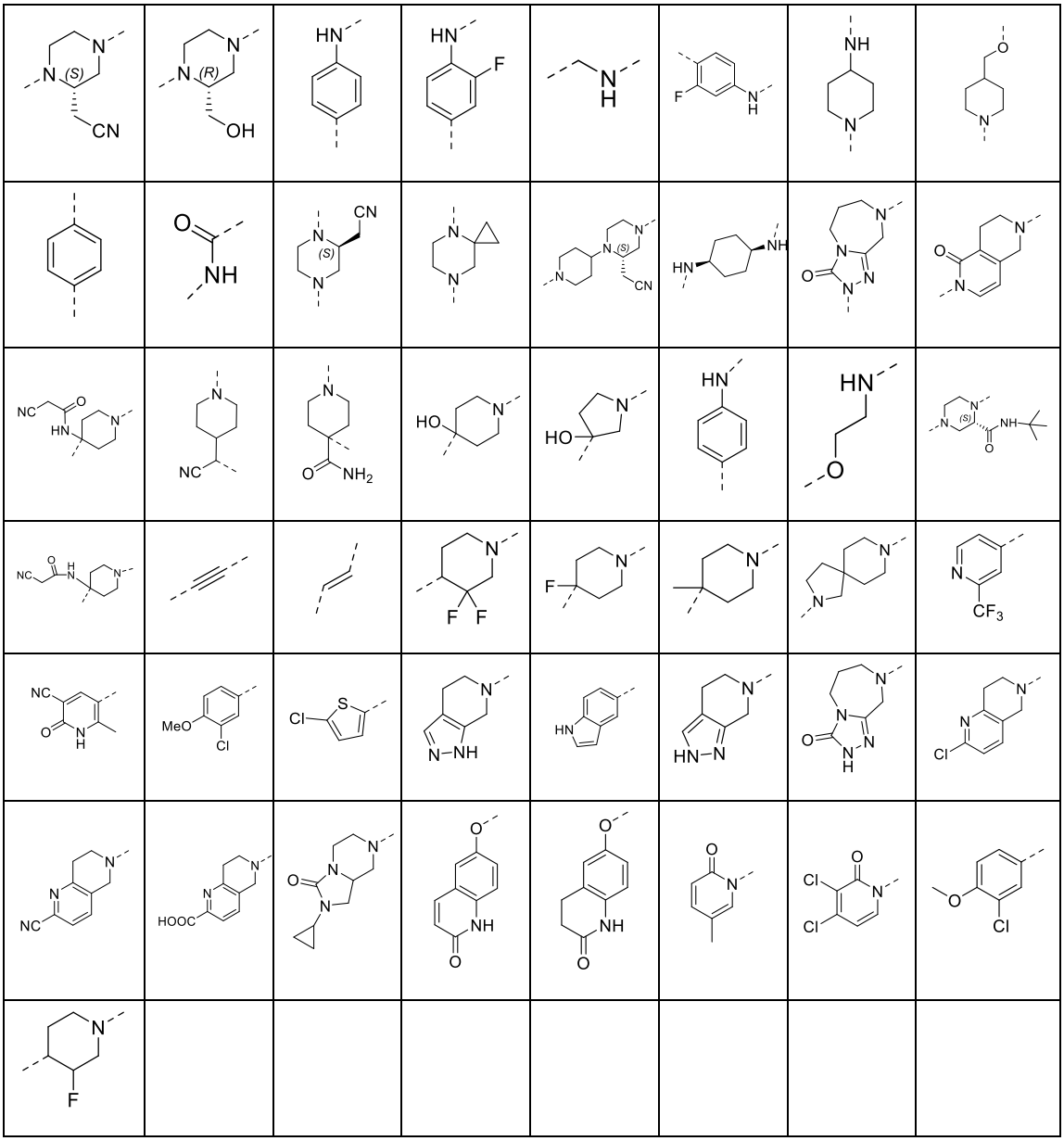
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

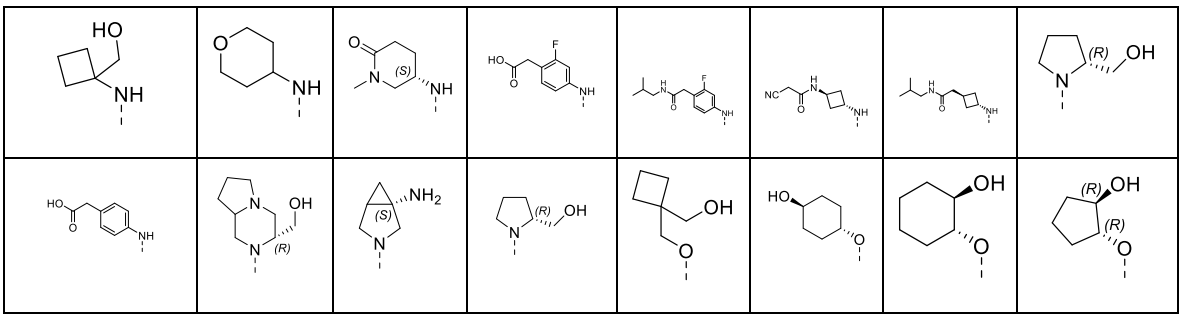
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$.

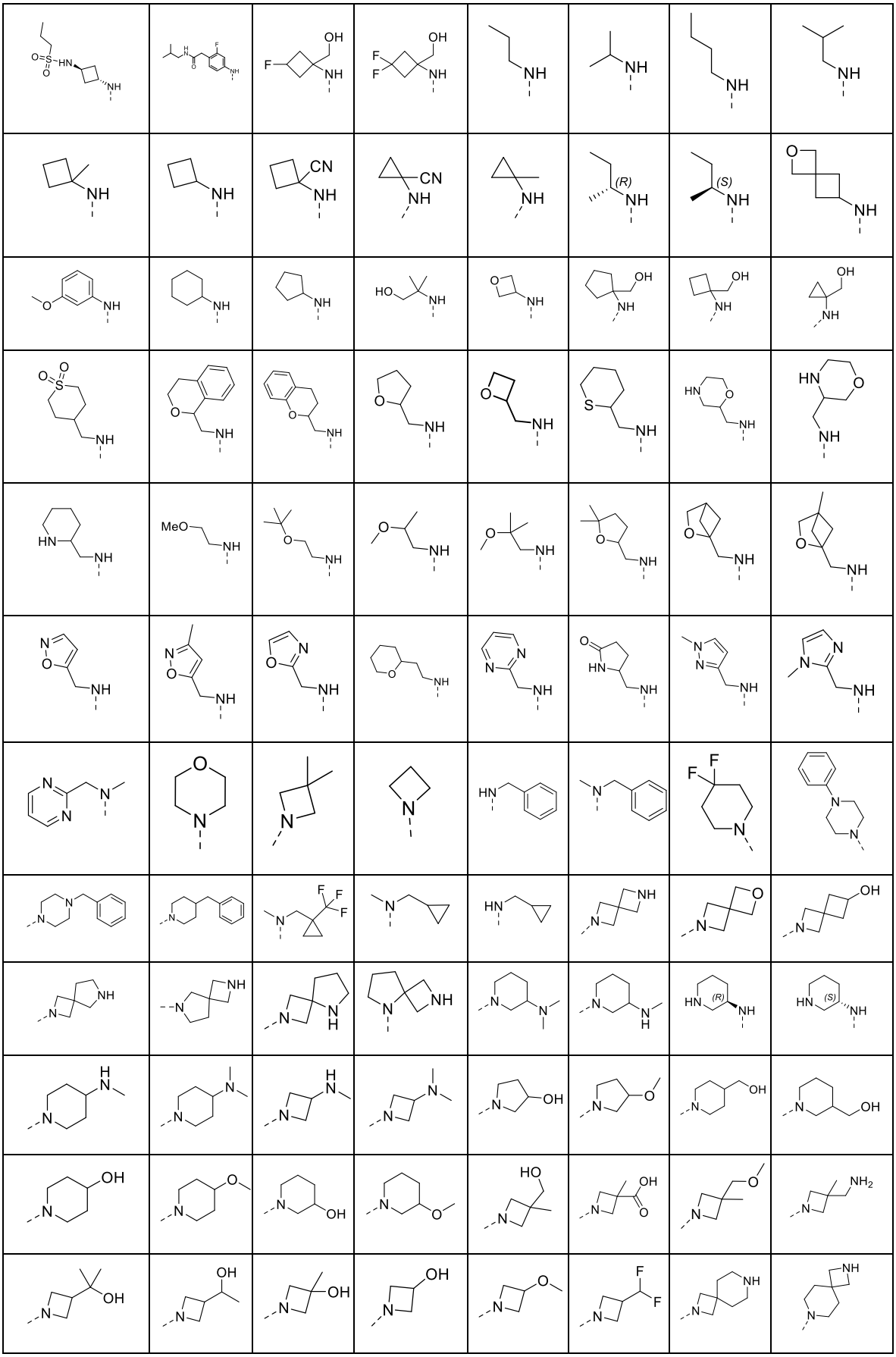
According to an embodiment of the present disclosure, examples of ring A may be selected from the following groups:

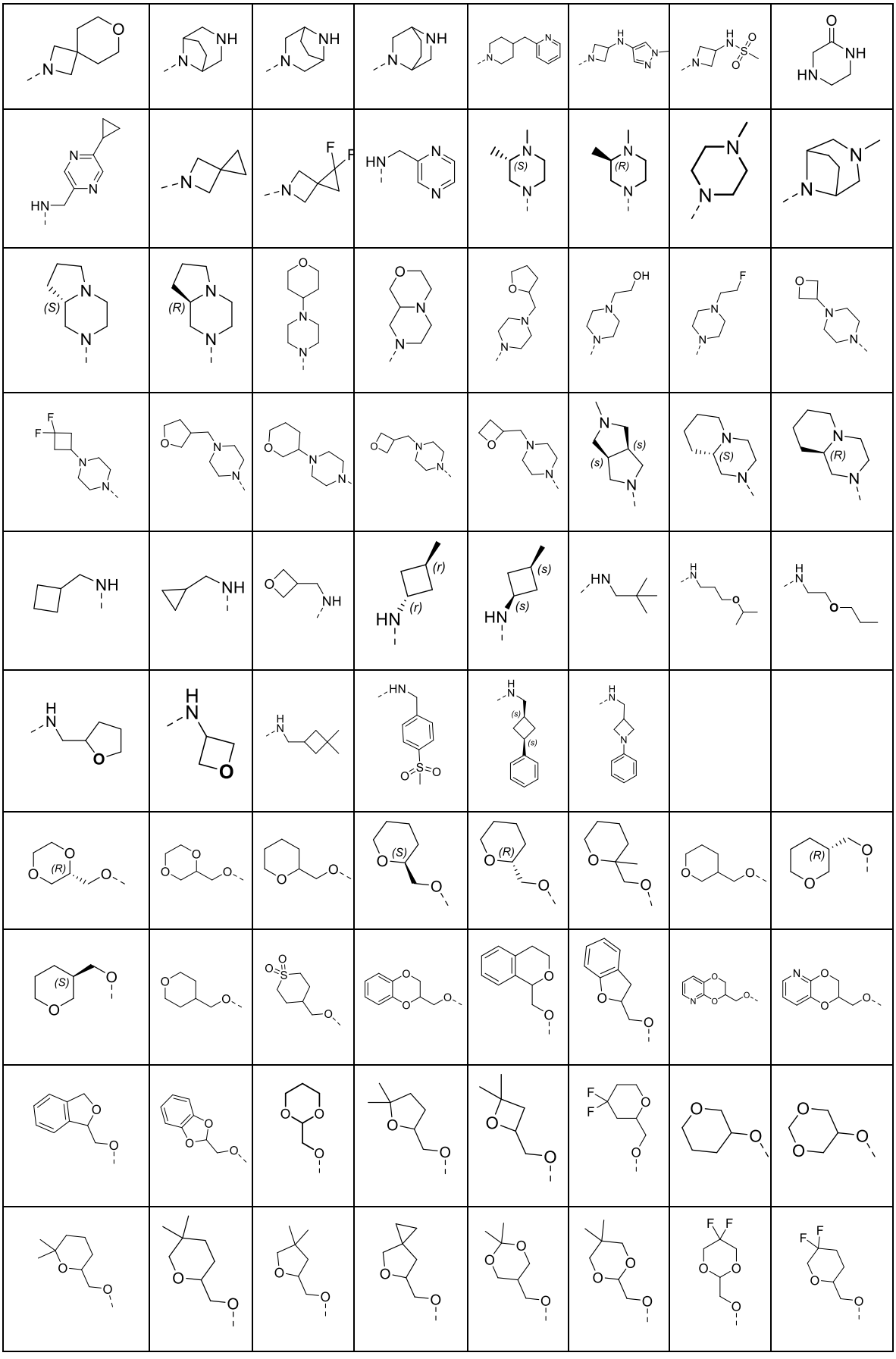


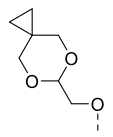
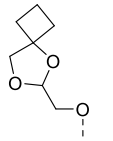
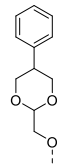
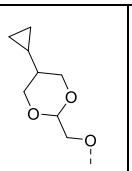
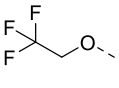
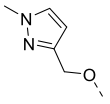
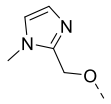
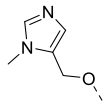
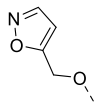
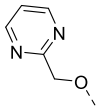
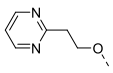
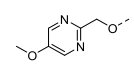
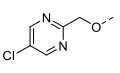
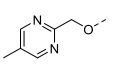
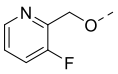
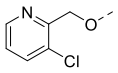
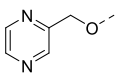
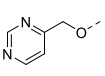
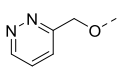
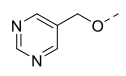
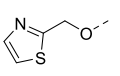
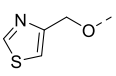
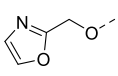
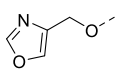
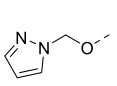
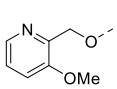
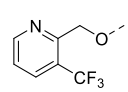
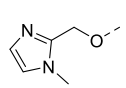
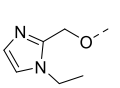
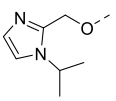
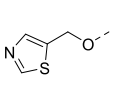
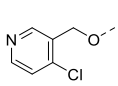
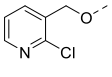
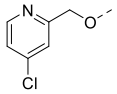
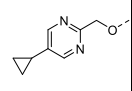
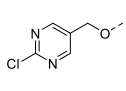
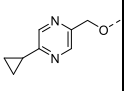
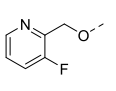
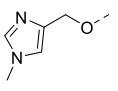
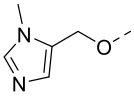


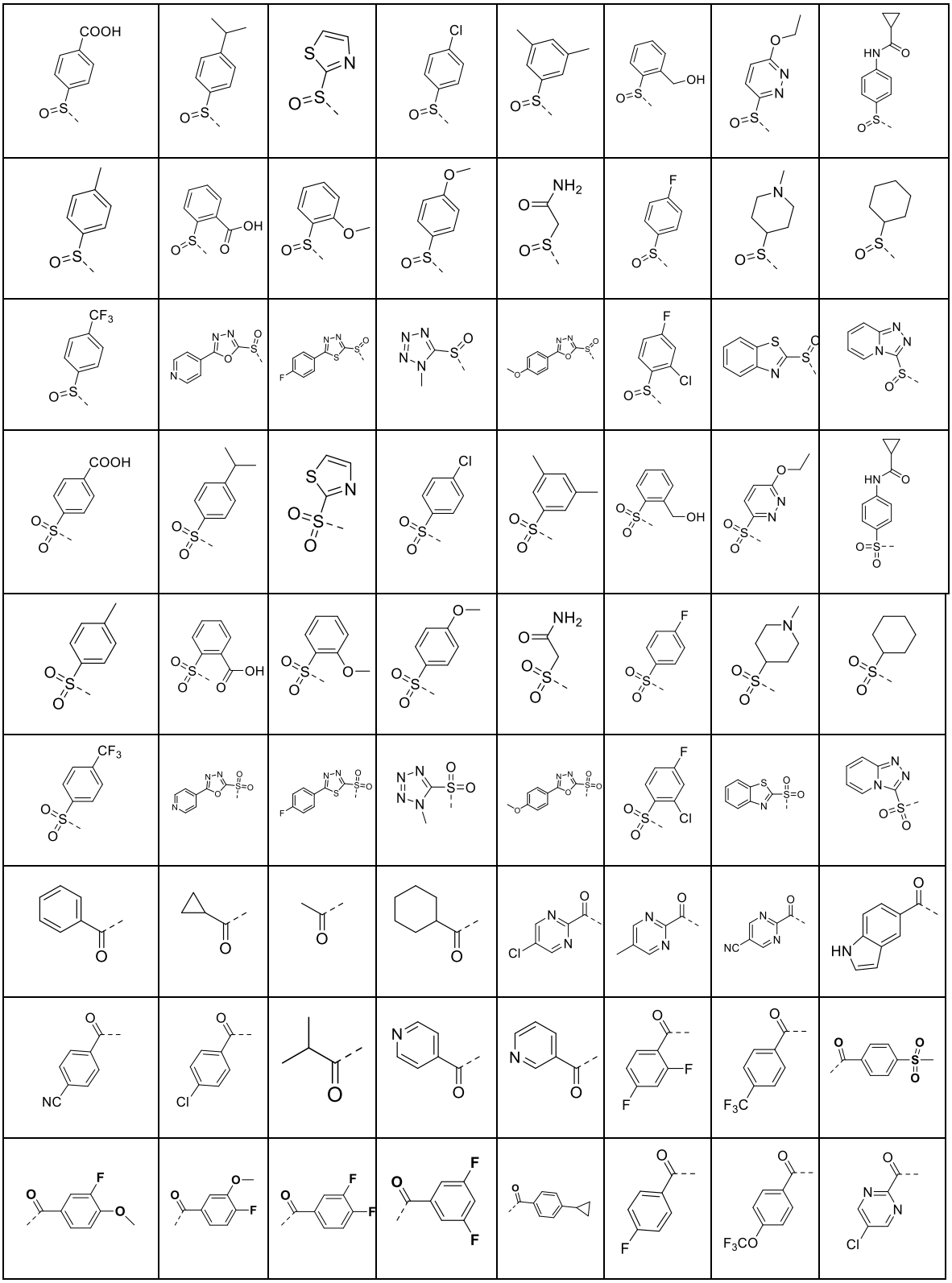
According to an embodiment of the present disclosure, examples of the substituent -W-R_2R_2, may be selected from the following groups:



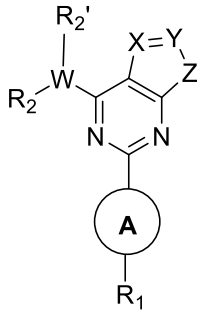






According to an embodiment of the present disclosure, the compound of formula VII has the following definitions:



VII

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3,

CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-

$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents is optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F,

$OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

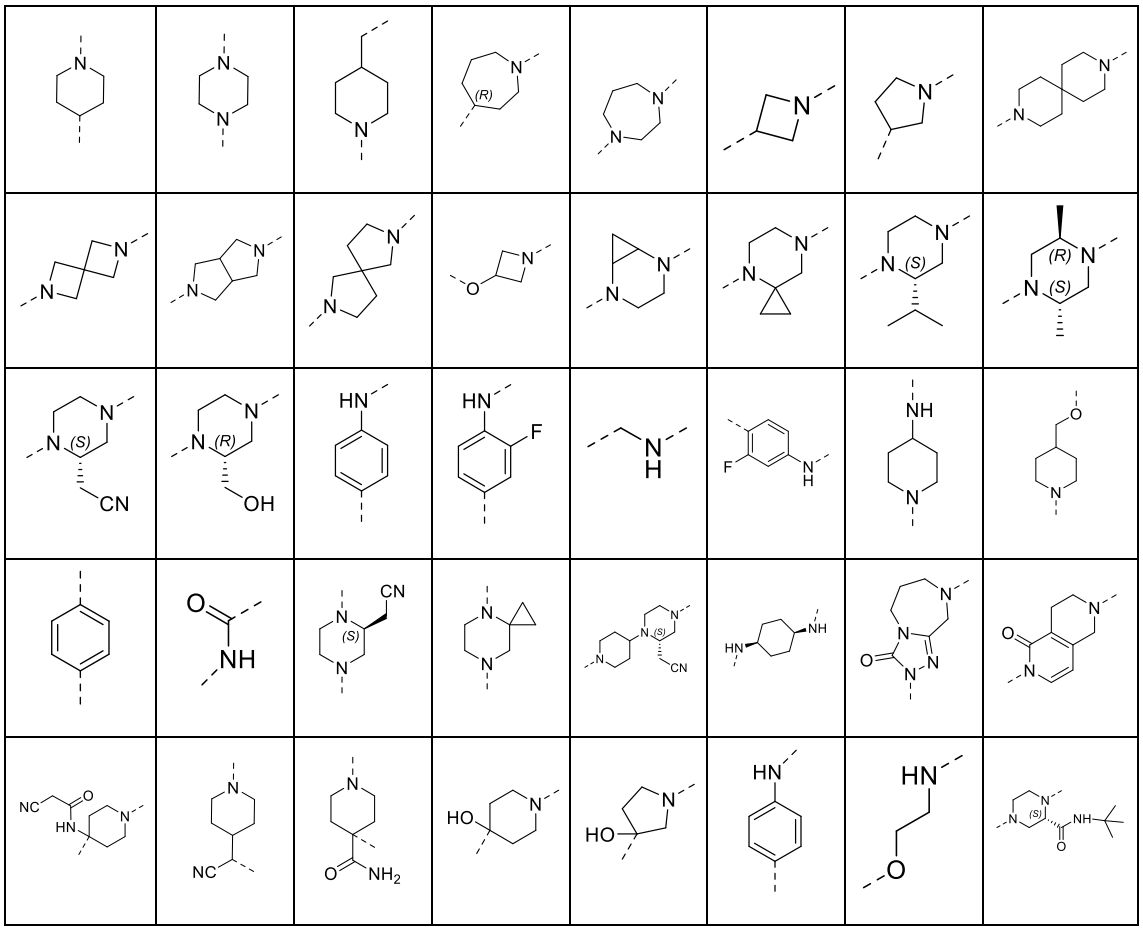
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

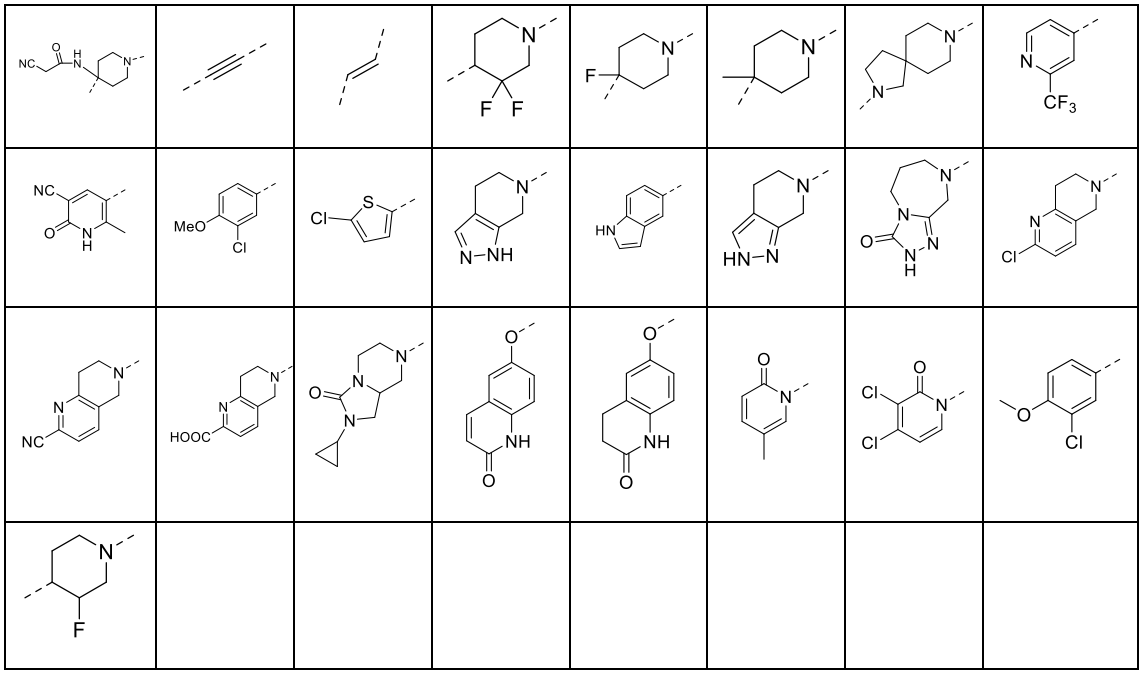
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

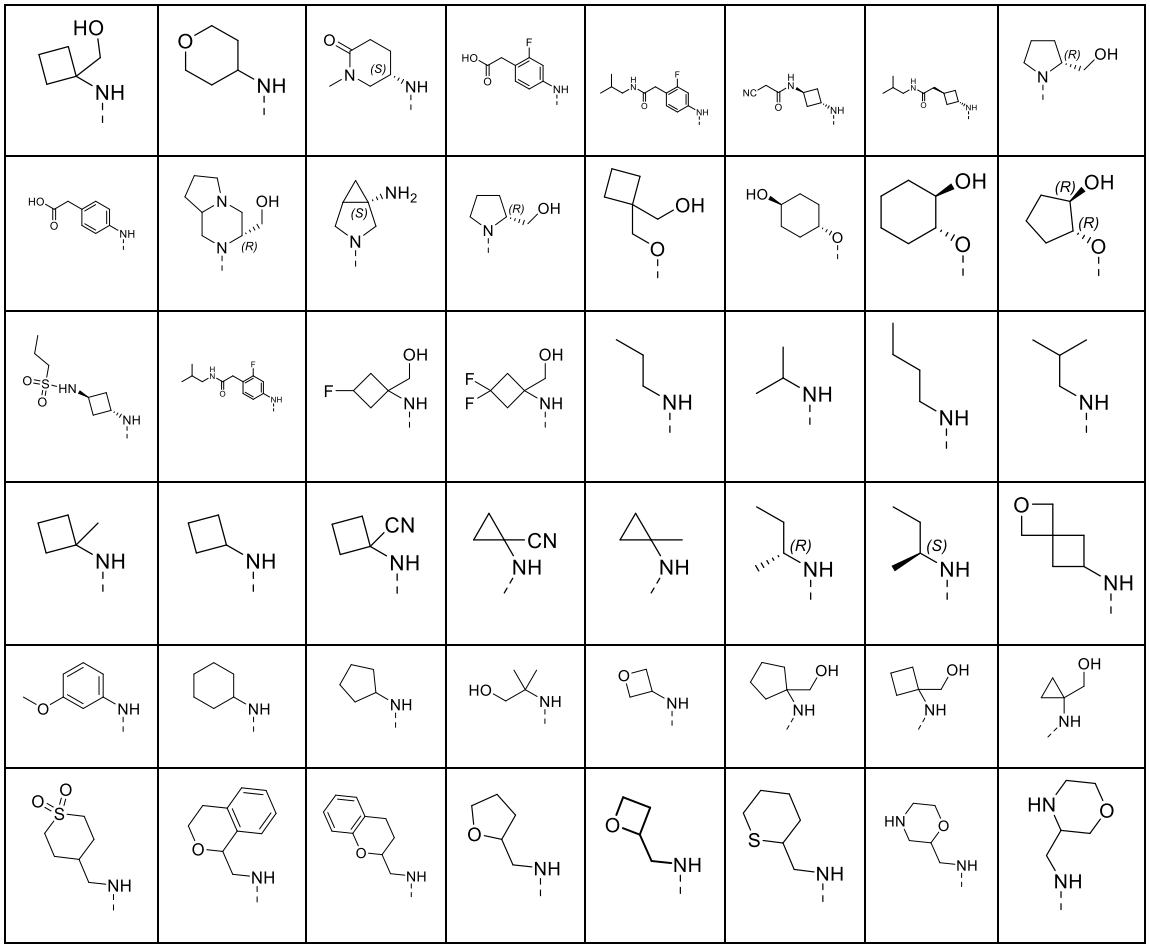
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$.

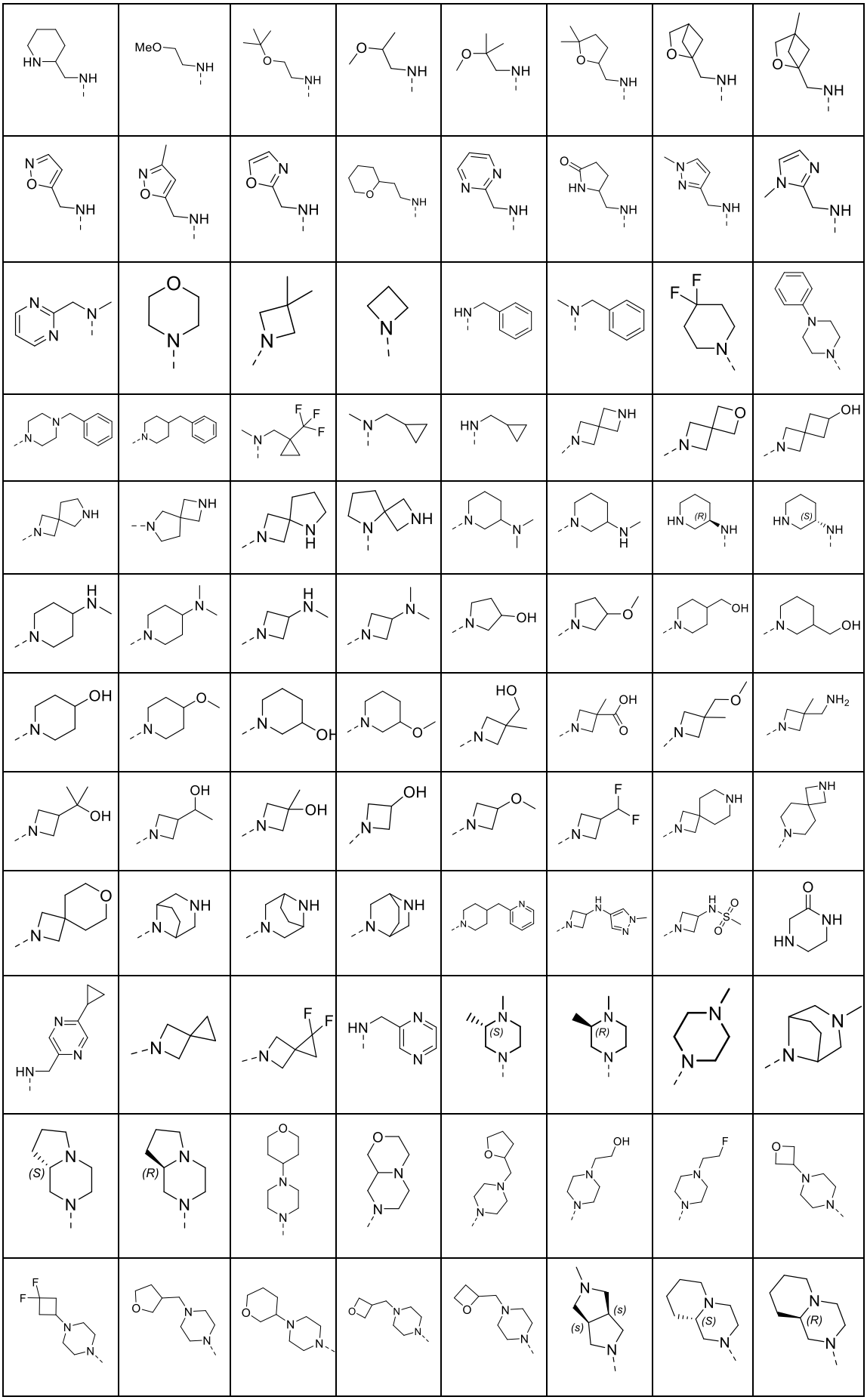
According to an embodiment of the present disclosure, examples of ring A may be selected from the following groups:

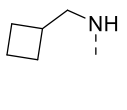
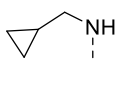
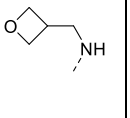
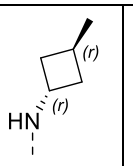
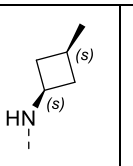
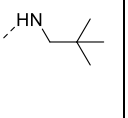
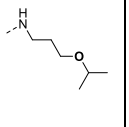
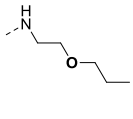
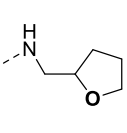
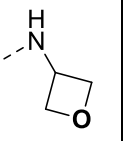
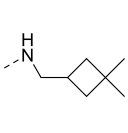
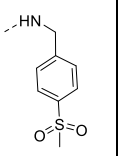
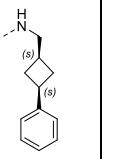
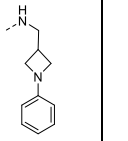
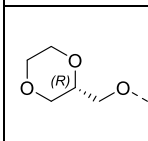
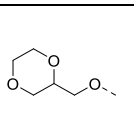
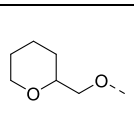
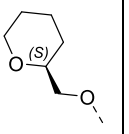
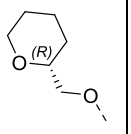
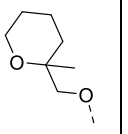
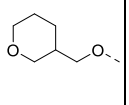
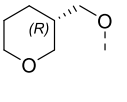
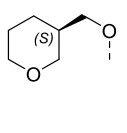
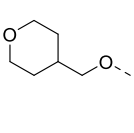
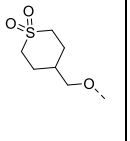
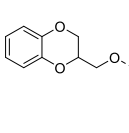
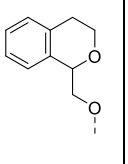
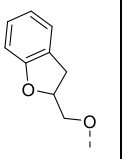
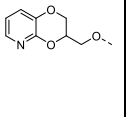
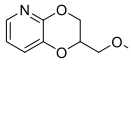
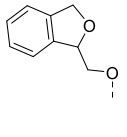
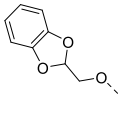
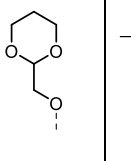
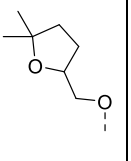
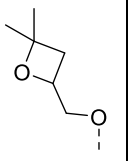
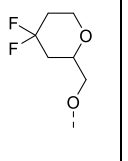
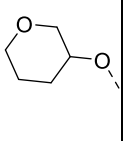
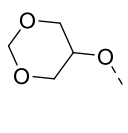
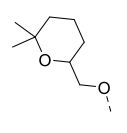
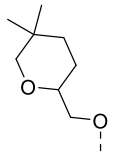


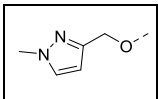
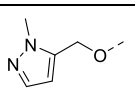
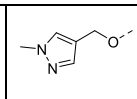
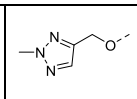
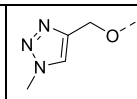
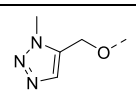
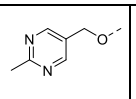
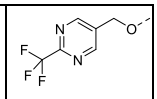
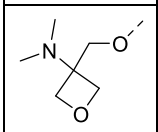
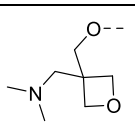
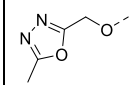
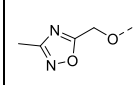
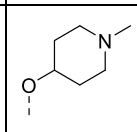
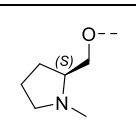
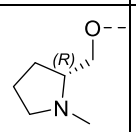
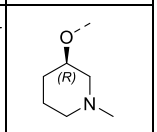
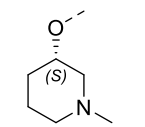
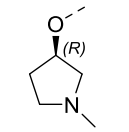
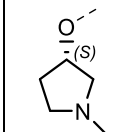
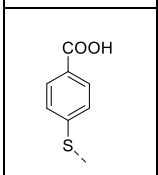
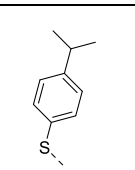
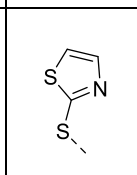
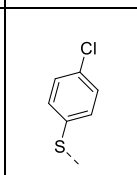
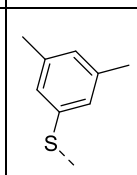
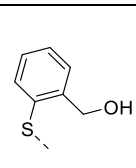
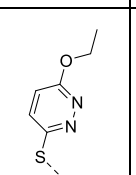
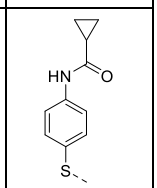
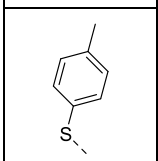
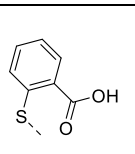
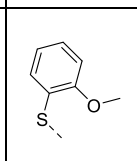
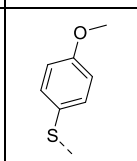
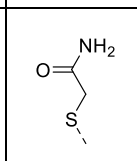
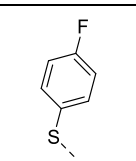
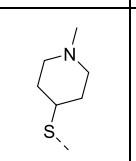
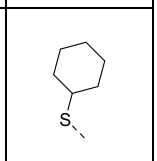
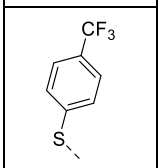
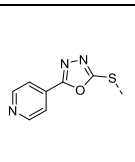
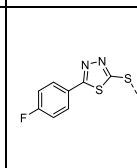
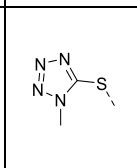
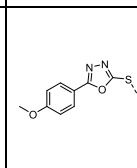


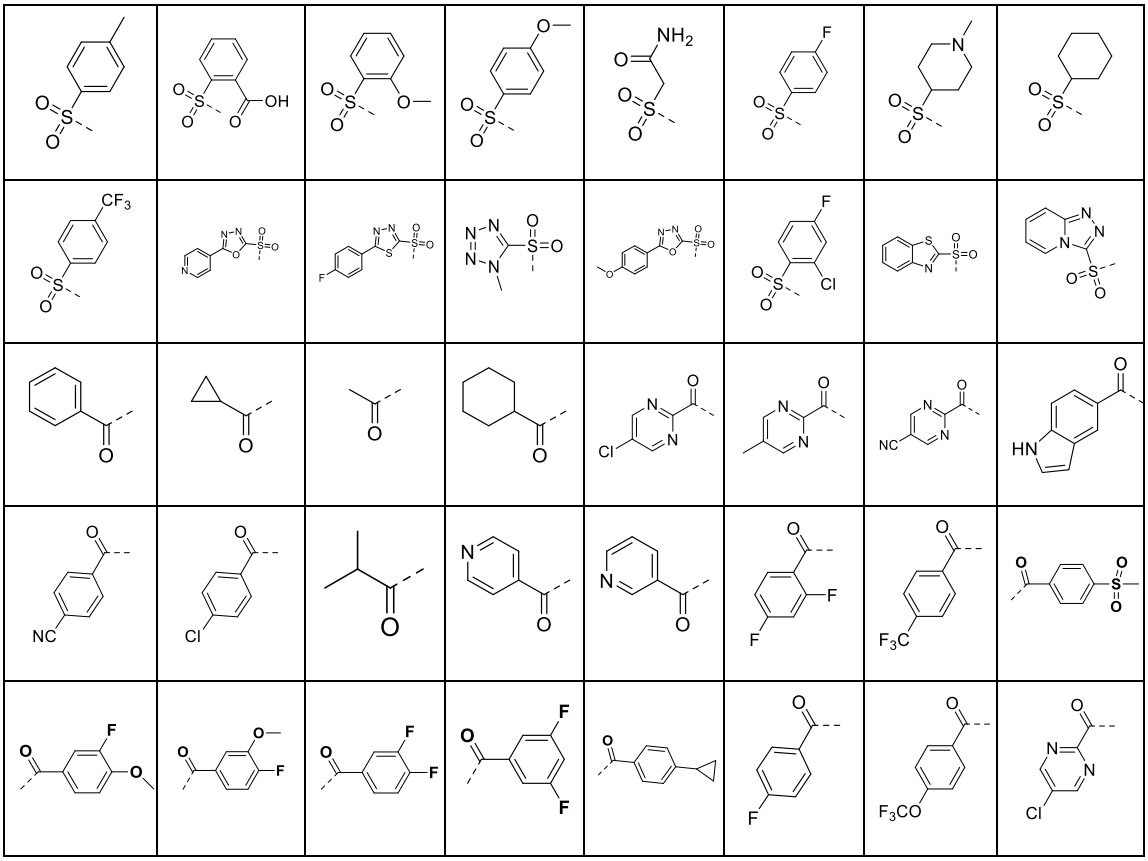
According to an embodiment of the present disclosure, examples of the group -W-$R_2R_{2'}$ may be selected from the following groups:



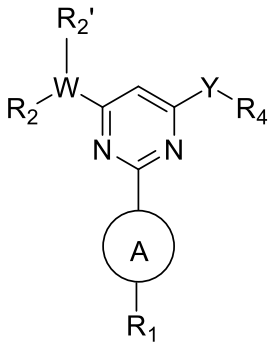




According to an embodiment of the present disclosure, the compound of formula VIII has the following definitions:



VIII

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), $C_{1\text{-}2}$ alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic $C_{6\text{-}20}$ aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$,

$CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, $C_{3\text{-}10}$ cycloalkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ fluoroalkyl, CF_3, CHF_2, CH_2F, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $C_{1\text{-}3}$ alkyl-$OR^{1.1}$, $SR^{1.1}$, $C_{1\text{-}3}$ alkyl-$SR^{1.1}$, $SO\text{-}R^{1.1}$, $C_{1\text{-}3}$ alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl alcohol, $C_{1\text{-}3}$ haloalkyl, a mono- or bicyclic ring, -$C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-($C_{1\text{-}3}$ alkyl), halogen, $C_{1\text{-}10}$ alkyl, and $C_{6\text{-}20}$ aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from $C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, $CO\text{-}NH_2$,

$CO\text{-}NH\text{-}CH_3$, $-CO\text{-}N(CH_3)_2$, $SO_2\text{-}(C_{1\text{-}3}$ alkyl), $CO\text{-}R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $COOR^{1.1}$;

R_2 represents hydrogen or a mono- or polycyclic $C_{6\text{-}20}$ aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $NR^{2.2}R^{2.3}$, $CH_2\text{-}NR^{2.2}R^{2.3}$, $CH_2CH_2\text{-}NR^{2.2}R^{2.3}$, $C_{3\text{-}10}$ cycloalkyl, a 3- to 20-membered heterocyclic ring, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ fluoroalkyl, CF_3, CHF_2, CH_2F, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}3}$ alkyl-$SOR^{2.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{2.1}$, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, $SR^{2.1}$, $C_{1\text{-}3}$ alkyl-$SR^{2.1}$, $SO\text{-}R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SOR^{2.1}$, $SO_2\text{-}R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl alcohol, $C_{1\text{-}3}$ haloalkyl, a mono- or bicyclic ring, $-C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl,

3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$;

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{6-20} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{6-20} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

R_4 represents a group selected from aryl and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or independently and optionally substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic

C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, $SO\text{-}R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

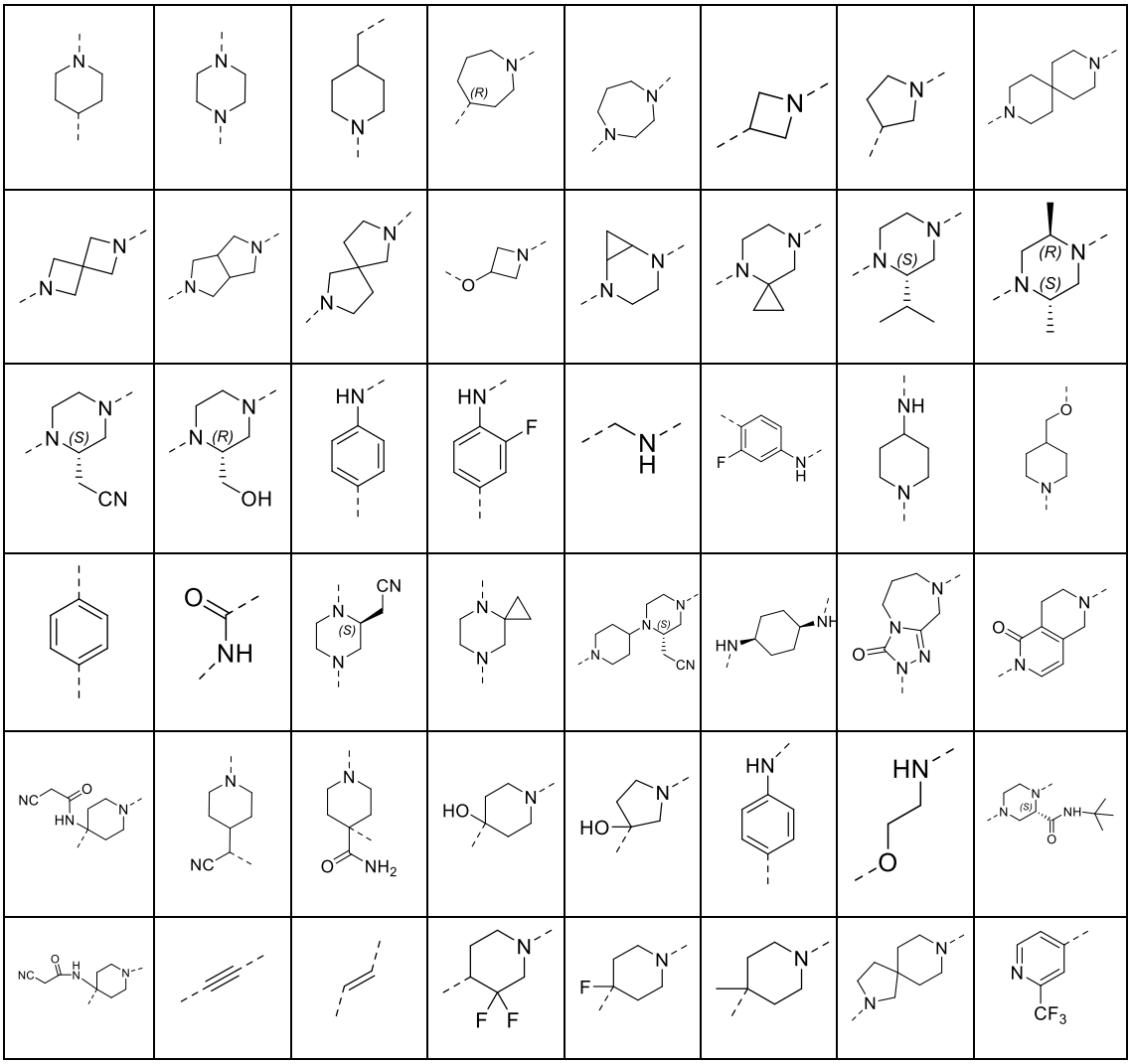
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

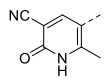
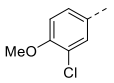
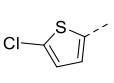
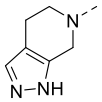
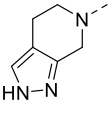
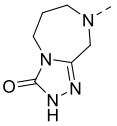
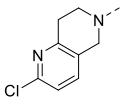
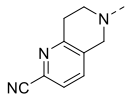
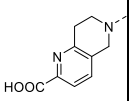
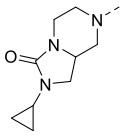
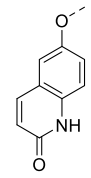
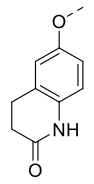
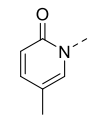
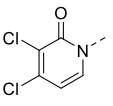
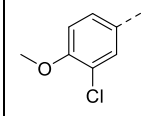
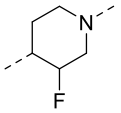
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

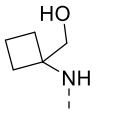
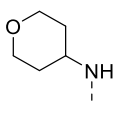
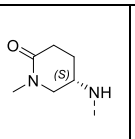
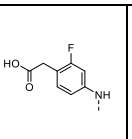
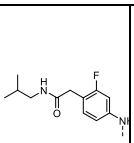
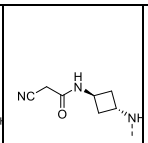
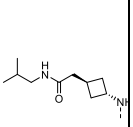
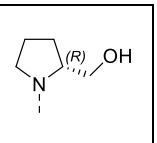
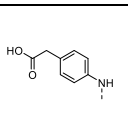
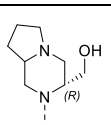
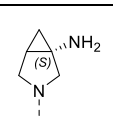
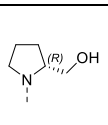
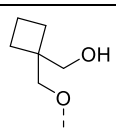
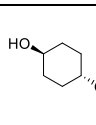
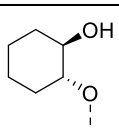
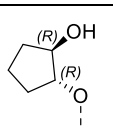
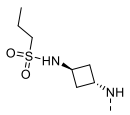
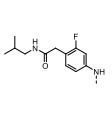
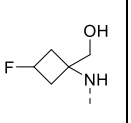
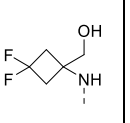
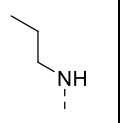
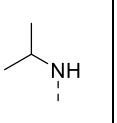
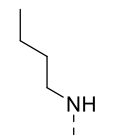
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$.

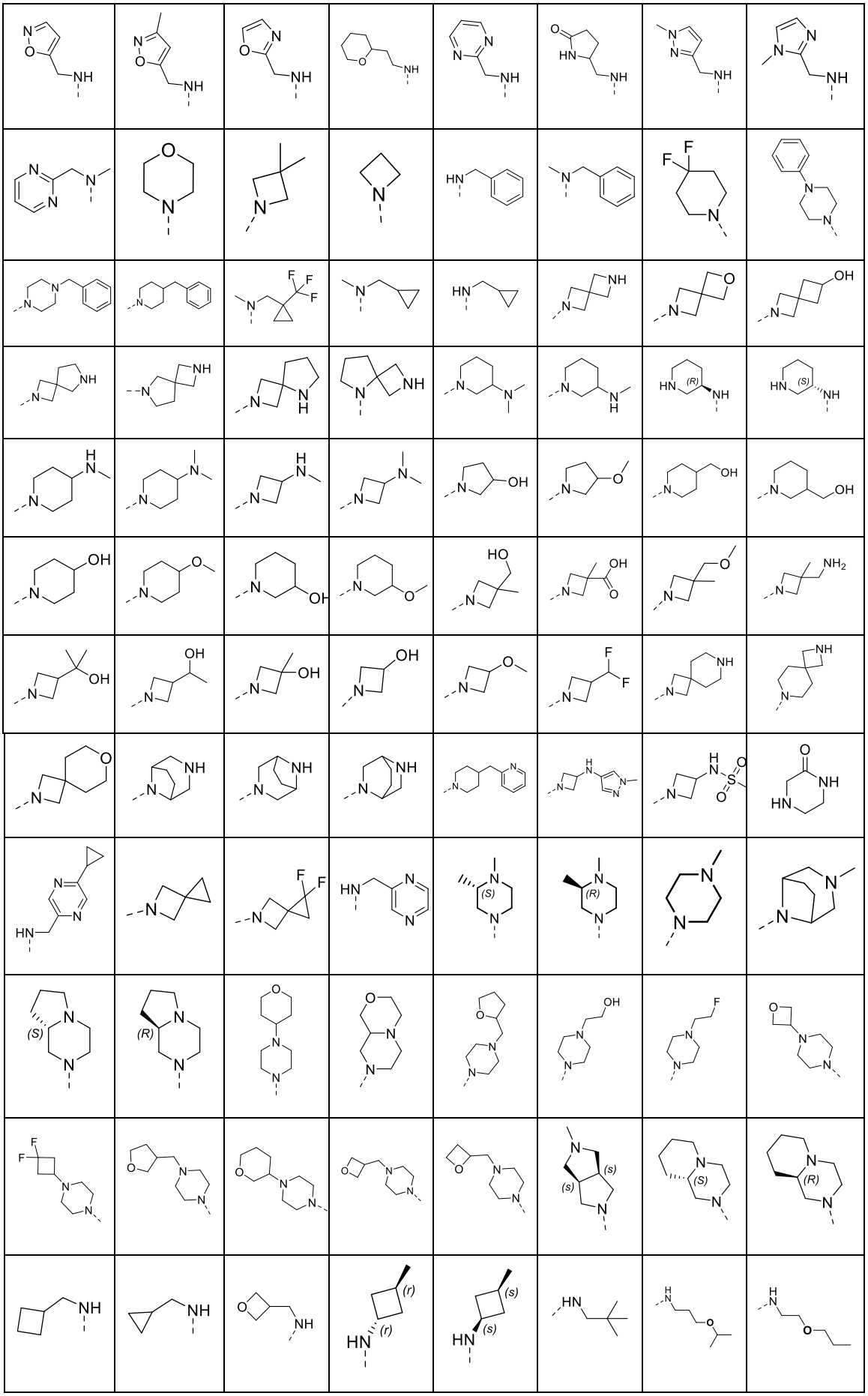
According to an embodiment of the present disclosure, examples of ring A may be selected from the following groups:

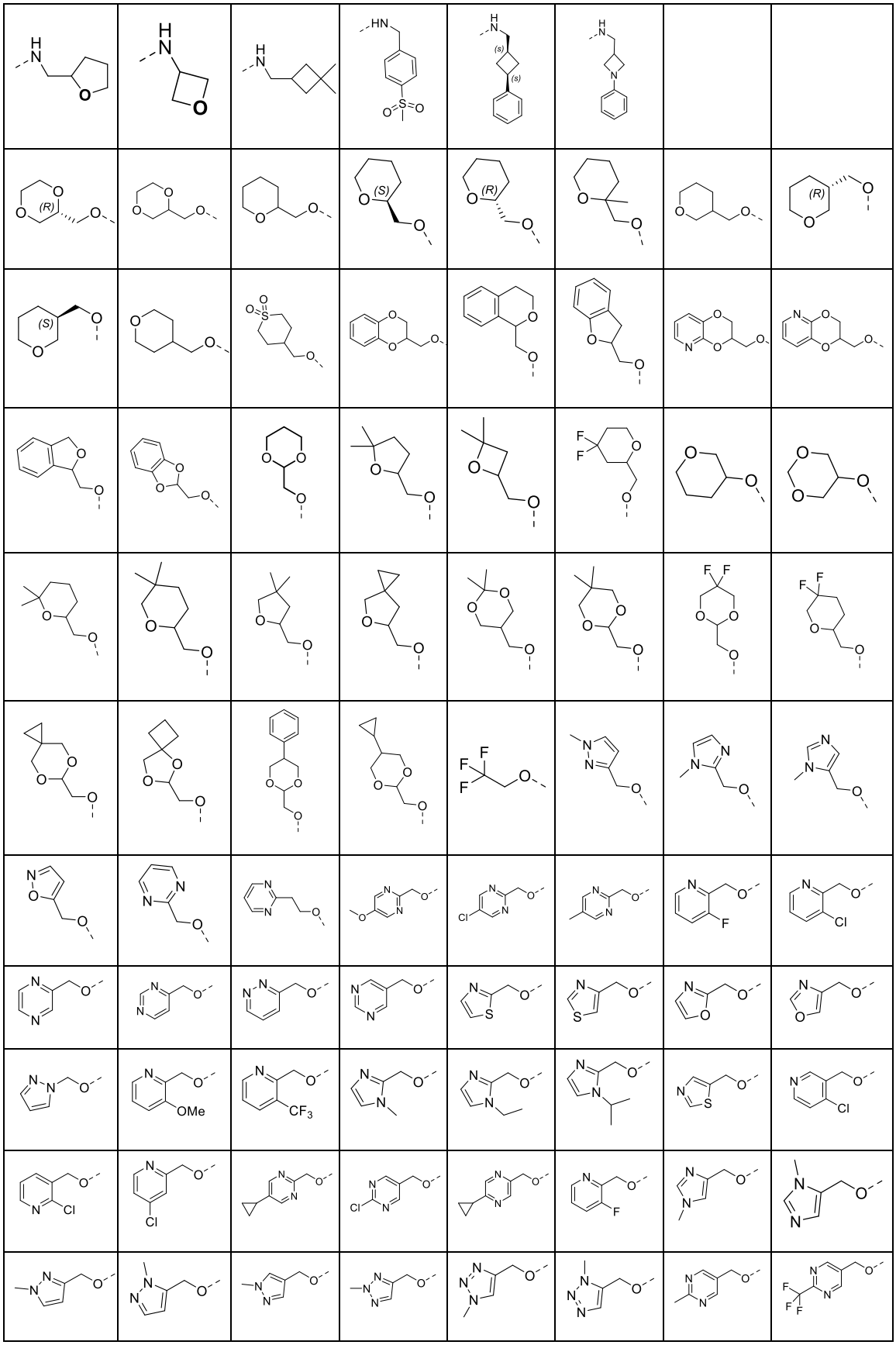


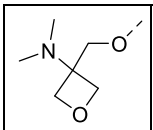
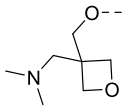
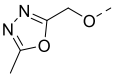
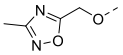
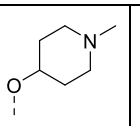
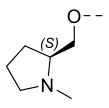
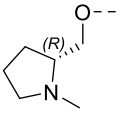
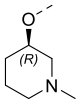
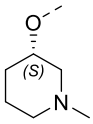
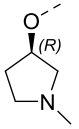
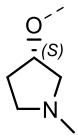
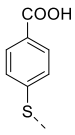
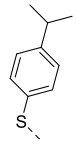
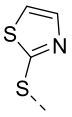
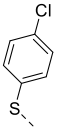
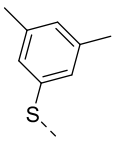
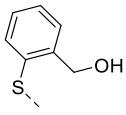
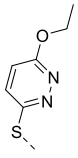
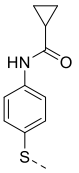
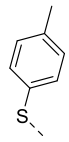
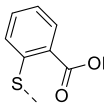
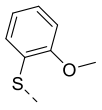
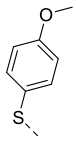
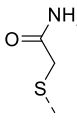
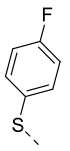
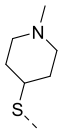
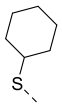
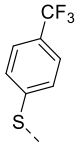
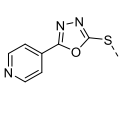
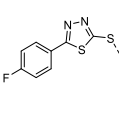
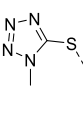
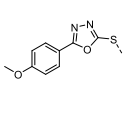
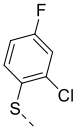
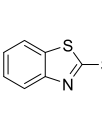
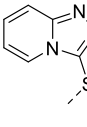
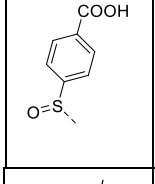
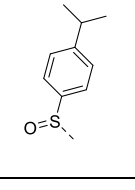
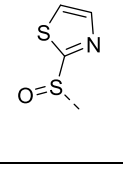
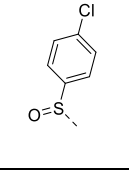
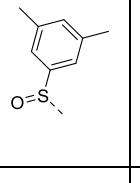
							
							
							

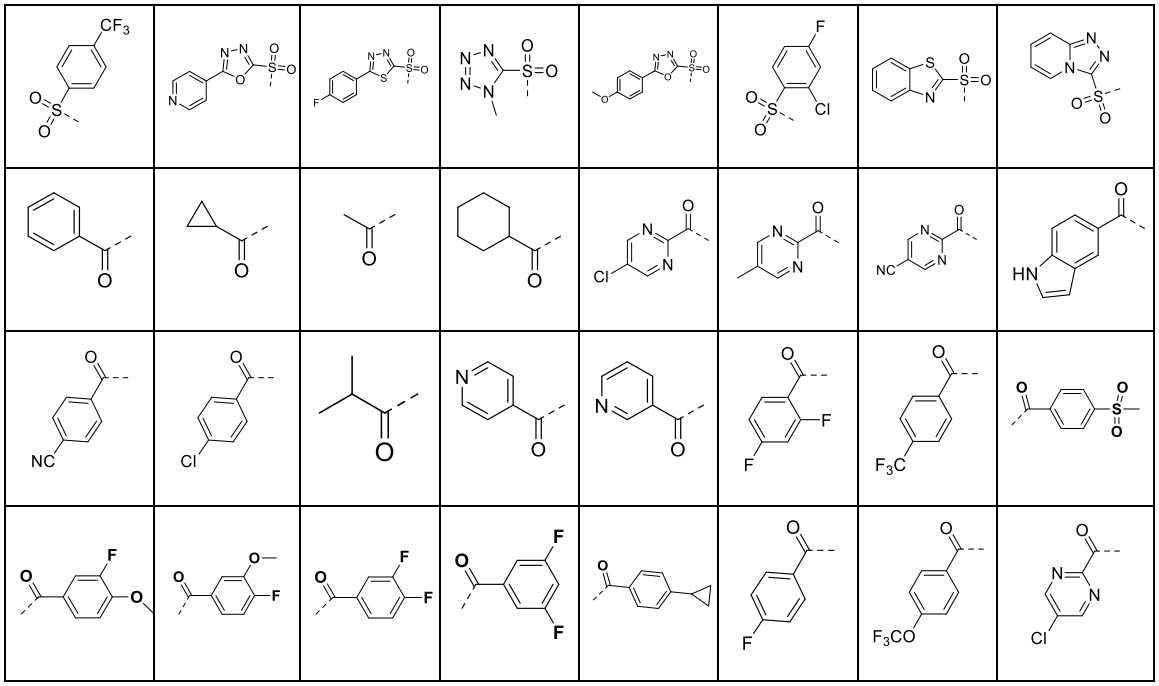
According to an embodiment of the present disclosure, examples of the group -W-$R_2R_{2'}$ may be selected from the following groups:

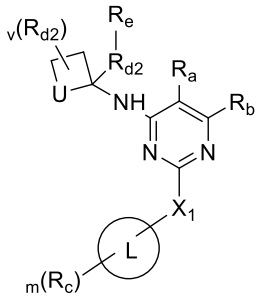






According to an embodiment of the present disclosure, the compound of formula IX has the following definitions:



IX

wherein:

X_1 represents a chemical bond, C_{1-20} alkylene, O, S, NR_q, S(=O), $S(=O)_2$, or C(=O);

U represents $-(CH_2)_t-$, O, S, NR_q, S(=O), $S(=O)_2$, or C(=O), wherein t represents 0, 1, 2, or 3;

R_q is selected from H, halogen, OH, CN, NO_2, NH_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, C_{1-8} heteroalkyl-fused C_{6-20} aryl-, C_{1-8} heteroalkyl-C_{6-20} aryl-, NH_2, $-C(O)R_{41}$,

-C(O)OR_{42}, -OC(O)R_{43}, -S(O)$_2R_{44}$, -S(O)$_2OR_{45}$, -OS(O)$_2R_{46}$, and -P(O)(OR_{47})(OR_{48});

v represents 0, 1, 2, 3, 4, or 5;

L represents a chemical bond, C_{2-20} alkynyl, or Cy, wherein L may be linked to X_1 or R_c at any position;

Cy represents a chemical bond, 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl, wherein the 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl may be optionally fused to 4- to 7-membered cycloalkyl, provided that when the heterocyclyl contains an N atom, the heterocyclyl may be bonded to the carbon atom at the 2-position of the pyrimidine ring in formula IX via the N atom or a C atom thereof;

R_a represents H or -X-R_3;

X represents CH_2, O, S, NH, -S(O)-, -S(O)$_2$-, or -C(O)-;

R_3 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d4}: C_{1-20} alkyl, -C(O)R_{61}, -C(O)OR_{62}, -OC(O)R_{63}, and NH_2;

R_b represents H or -Y-R_4;

Y represents CH_2, O, S, NH, -S(O)-, -S(O)$_2$-, or -C(O)-;

R_4 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d5}: C_{1-20} alkyl, -C(O)R_{61}, -C(O)OR_{62}, -OC(O)R_{63}, and NH_2;

provided that R_a and R_b are not both H;

or R_a and R_b, together with the atoms linked thereto, form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d6}: C_{5-20} cycloalkenyl, 3- to 20-membered heterocyclyl, 5- to 20-membered heteroaryl, and 6- to 20-membered aryl;

R_{d2}, R_{d4}, R_{d5}, and R_{d6} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), SO, SO_2, and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, -C(O)R_{31}, -CH_2-C(O)R_{31}, -C(O)OR_{32}, -CH_2C(O)OR_{32}, -C(O)NHR_{32}, -CH_2C(O)NHR_{32}, -OC(O)R_{33}, -S(O)$_2R_{34}$, -S(O)$_2OR_{35}$, -OS(O)$_2R_{36}$, and -P(O)(OR_{37})(OR_{38});

or when two or more substituents selected from R_{d2}, R_{d4}, R_{d5}, and R_{d6} are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_c are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl-O-C_{6-20} aryl-, 5- to 20-membered heteroaryl-N-C_{6-20} aryl-, 5- to 20-membered heteroaryl-S-C_{6-20} aryl-, 5- to 20-membered heteroaryl-CH_2-C_{6-20} aryl-, C_{4-10} cycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-fused C_{6-20} aryl-, C_{4-10} cycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl, C_{4-10} cycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-fused 5- to 20-membered heteroaryl-, C_{4-10} cycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-5- to 20-membered heteroaryl-, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, -C(O)R_{31}, -C(O)OR_{32}, -OC(O)R_{33}, -S(O)$_2R_{34}$, -S(O)$_2$OR_{35}, -OS(O)$_2R_{36}$, and -P(O)(OR_{37})(OR_{38});

for example, the 4- to 10-membered heterocycloalkyl or 4- to 10-membered heterocycloalkenyl may be: 1-methylpyrrolidinyl, 1-ethylpyrrolidinyl, 1-cyclopropylpyrrolidinyl, 1-cyclopropylmethylpyrrolidinyl, 5-methyl-4,5-dihydropyridazin-3(2H)-one, 1-methylazetidinyl, or 1-methylpiperidinyl;

m is selected from integers from 1 to 10;

R_e are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, NH_2, oxo (=O), thio (=S), O-$CONH_2$, O-$CONHR_f$, and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy,

C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, C_{1-8} heteroalkyl-fused C_{6-20} aryl-, C_{1-8} heteroalkyl-C_{6-20} aryl-, NH_2, $-C(O)R_{41}$, $-C(O)OR_{42}$, $-OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

or when two or more substituents selected from R_e are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_f are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{51}$, $-C(O)OR_{52}$, $-OC(O)R_{53}$, $-S(O)_2R_{54}$, $-S(O)_2OR_{55}$, $-OS(O)_2R_{56}$, and $-P(O)(OR_{57})(OR_{58})$;

or when two or more substituents selected from R_f are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_g are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, and R_{58} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3-

to 20-membered heterocyclyl, and NH_2;

the 3- to 20-membered heterocyclyl represents a saturated or unsaturated non-aromatic ring or ring system; for example, it is a 4-, 5-, 6-, or 7-membered monocyclic ring system, a 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic (e.g., fused, bridged, or spiro) ring system, or a 10-, 11-, 12-, 13-, 14-, or 15-membered tricyclic ring system, and contains at least one, e.g., 1, 2, 3, 4, 5, or more heteroatoms independently selected from O, S, and N, wherein N and S may also be optionally oxidized to various oxidized forms to form nitrogen oxides, -S(O)-, or -$S(O)_2$-;

the C_{6-20} aryl represents an aromatic or partially aromatic monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic hydrocarbon ring having 6-20 carbon atoms, which may be a single aromatic ring or multiple aromatic rings fused together;

the 5- to 20-membered heteroaryl represents a monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic aromatic ring system, wherein the aromatic ring system has 5-20 ring atoms and contains 1, 2, 3, 4, 5, or more heteroatoms independently selected from N, O, and S.

According to an embodiment of the present disclosure, L represents alkynyl, a mono- or polycyclic C_{6-20} aryl group, or mono- or polycyclic C_{6-20} aryl-fused 4- to 7-membered cycloalkyl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{1.1}$, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

L represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$,

$CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 10-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 10-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents is optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

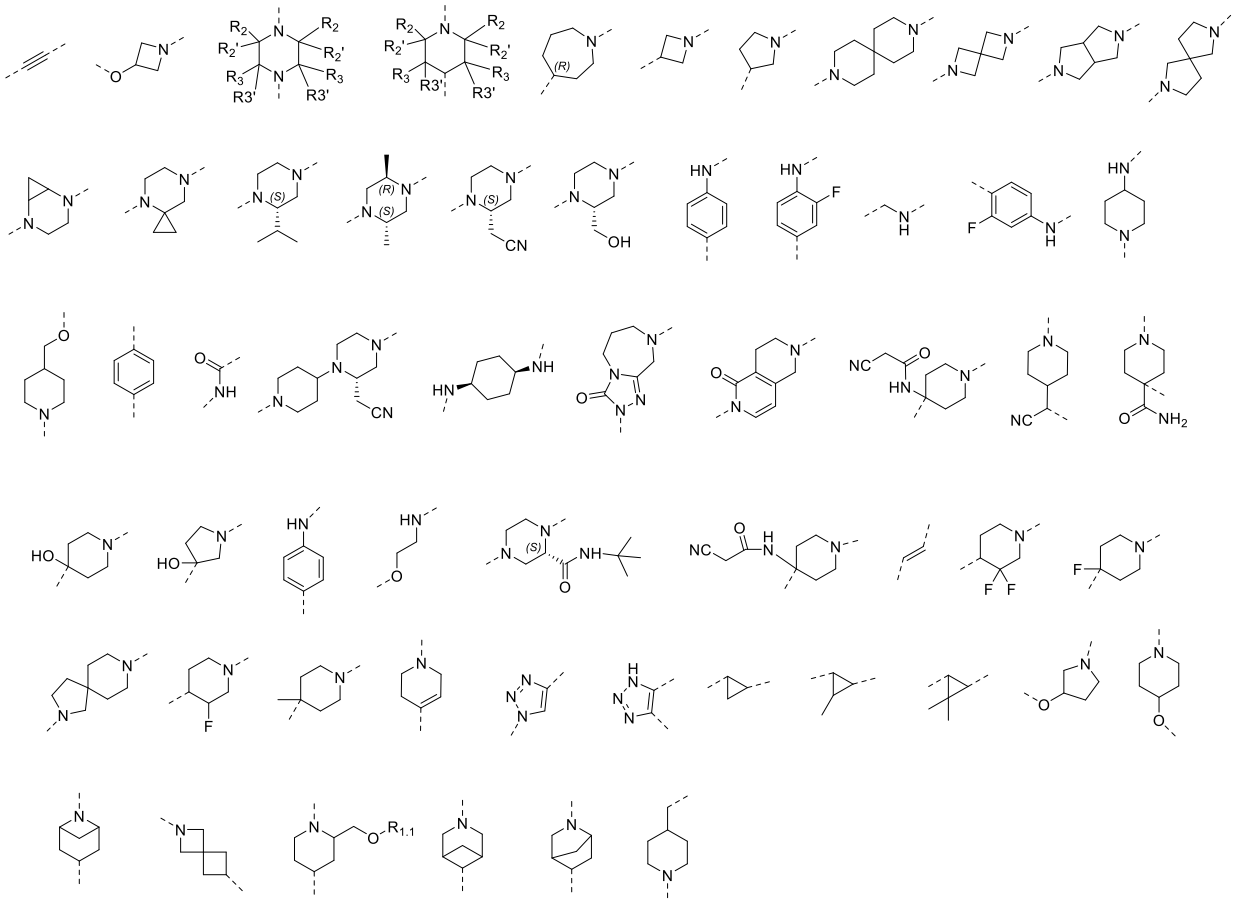
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O; in some embodiments, L is selected from 5-membered monocyclic heteroaryl, a 5-membered heteroaryl-fused phenyl ring, 5-membered heteroaryl-fused 5- to 10-membered heteroaryl, 5-membered heteroaryl-fused 4- to 7-membered cycloalkyl, 5-membered heteroaryl-fused 4- to 7-membered heterocycloalkyl, 6-membered heteroaryl-fused phenyl ring, 6-membered heteroaryl-fused 5- to 10-membered heteroaryl, 6-membered heteroaryl-fused 6-membered heteroaryl, 6-membered heteroaryl-fused 4- to 7-membered cycloalkyl, and 6-membered heteroaryl-fused 4- to 7-membered heterocycloalkyl;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl alcohol, $C_{1\text{-}3}$ haloalkyl, $C_{3\text{-}11}$ mono- or bicyclic heterocyclic ring, -$C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, 3- to 10-membered heterocyclic-$C_{1\text{-}6}$ alkyl, $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-($C_{1\text{-}3}$ alkyl), halogen, $C_{1\text{-}10}$ alkyl, and $C_{6\text{-}20}$ aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from $C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkylene, mono- or bicyclic $C_{6\text{-}20}$ aryl, a 3- to 10-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-($C_{1\text{-}3}$ alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $COOR^{1.1}$.

According to an embodiment of the present disclosure, examples of L may be selected from the following groups:



According to an embodiment of the present disclosure, R_{d2} are identical or different, and each independently represent hydrogen, halogen, cyano, hydroxyl, CF_3, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CHF_2, CH_2F, SO_2-CH_3, SO_2-CH_2CH_3, SO_2-$NR^{1.2}R^{1.3}$, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, or C_{1-3} alkyl-$NHR^{1.1}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$.

According to an embodiment of the present disclosure, R_e may be selected from OH;

R_{d6} are identical or different, and each independently represent H, F, Me, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{1.1}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, mono- or polycyclic C_{6-20} aryl, mono- or polycyclic C_{6-20} aryl-fused 4- to 7-membered cycloalkyl, mono- or polycyclic C6-20 heteroaryl-fused 4- to 7-membered cycloalkyl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl; or

R_{d6} are identical or different, and each independently represent H, F, Me, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{1.1}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or two R_{d6}, together with the atom linked thereto, form 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged cycloalkyl, or a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.22.3}$;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$.

R_c are identical or different, and each independently represent hydrogen, a mono- or polycyclic C_{6-20} aryl group, or mono- or polycyclic C_{6-20} aryl-fused 4- to 7-membered cycloalkyl, for example, C_{4-10} cycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-fused C_{6-20} aryl-, C_{4-10} cycloalkyl-C_{6-20} aryl-, 4-

to 10-membered heterocycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl, C_{4-10} cycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-fused 5- to 20-membered heteroaryl-, C_{4-10} cycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-5- to 20-membered heteroaryl-, or 4- to 10-membered heterocycloalkenyl-5- to 20-membered heteroaryl-, or are selected from 5- to 20-membered heteroaryl-O-C_{6-20} aryl-, 5- to 20-membered heteroaryl-N-C_{6-20} aryl-, 5- to 20-membered heteroaryl-S-C_{6-20} aryl-, and 5- to 20-membered heteroaryl-CH_2-C_{6-20} aryl-, wherein the above groups may be each independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituent of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{4.1}$, $COOR^{4.1}$ $CH_2COOR^{4.1}$, $CH_2CH_2COOR^{4.1}$, $CH{=}CHCOOR^{4.1}$, $CO\text{-}NR^{4.1}$ $CH_2CO\text{-}NR^{4.1}$, $CH_2CH_2CO\text{-}NR^{4.1}$, $CH{=}CHCO\text{-}NR^{4.1}$, $NR^{4.2}R^{4.3}$, $CH_2\text{-}NR^{4.2}R^{4.3}$, $CH_2CH_2\text{-}NR^{4.2}R^{4.3}$, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{4.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{4.1}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{4.2}R^{4.3}$;

or R_c are identical or different, and each independently represent a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{4.1}$, C_{1-3} alkyl-$OR^{4.1}$, $SR^{4.1}$, C_{1-3} alkyl-$SR^{4.1}$, $SO\text{-}R^{4.1}$, C_{1-3} alkyl-$SOR^{4.1}$, $SO_2\text{-}R^{4.1}$, C_{1-3} alkyl-$SO_2R^{4.1}$, $COOR^{4.1}$, $CH_2COOR^{4.1}$, $CH_2CH_2COOR^{4.1}$, $CH{=}CHCOOR^{4.1}$, $CO\text{-}NR^{4.1}$ $CH_2CO\text{-}NR^{4.1}$, $CH_2CH_2CO\text{-}NR^{4.1}$, $CH{=}CHCO\text{-}NR^{4.1}$, $COR^{4.1}$, $CH_2COR^{4.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{4.1}$, and $NR^{4.2}R^{4.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{4.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{4.2}R^{4.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused,

heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O; in some embodiments, R_4 is selected from 5-membered monocyclic heteroaryl, a 5-membered heteroaryl-fused phenyl ring, 5-membered heteroaryl-fused 5- to 10-membered heteroaryl, 5-membered heteroaryl-fused 4- to 7-membered cycloalkyl, 5-membered heteroaryl-fused 4- to 7-membered heterocycloalkyl, 6-membered heteroaryl-fused phenyl ring, 6-membered heteroaryl-fused 5- to 10-membered heteroaryl, 6-membered heteroaryl-fused 6-membered heteroaryl, 6-membered heteroaryl-fused 47-membered cycloalkyl, and 6-membered heteroaryl-fused 4- to 7-membered heterocycloalkyl;

the cycloalkyl may be saturated or partially saturated;

$R^{4.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{5-10} aryl;

$R^{4.2}$ and $R^{4.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{4.1}$, and $COOR^{4.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{4.1}$.

For example, the 4- to 10-membered heterocyclyl or 4- to 10-membered heterocycloalkenyl may be: 1-methylpyrrolidinyl, 1-ethylpyrrolidinyl, 1-cyclopropylpyrrolidinyl, 1-cyclopropylmethylpyrrolidinyl, 5-methyl-4,5-dihydropyridazin-3(2H)-one, 1-methylazetidinyl, or 1-methylpiperidinyl.

Or, according to the compound represented by formula H or formula G of the present disclosure (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof, when present, R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3}-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=$CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$,

CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, CN, C_{1-3} alkyl-CN, -SH, -NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3} alkyl-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, -$OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$, wherein $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$ have the definitions described in the context of the present disclosure.

Or, according to the compound represented by formula H or formula G of the present disclosure (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof, when present, R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, CN, NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, nitro, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CHCOO$R^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, CN, C_{1-3} alkyl-CN, -SH, -NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3} alkyl-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$, wherein $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$ have the definitions described in the context of the present disclosure.

Or, according to the compound represented by formula H or formula G of the present disclosure (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer,

the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof, when present, R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $C(CH_3)_2COOR^{2.1}$, $CF_2COOR^{2.1}$, $CHFCOOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}$, $CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $NR^{2.2}R^{2.3}$, $CH_2\text{-}NR^{2.2}R^{2.3}$, $CH_2CH_2\text{-}NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, $COOR^{2.1}$-C_{3-8} cycloalkyl, $CO\text{-}NR^{2.1}$-C_{3-8} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and $SO_2\text{-}NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, CN, C_{1-3} alkyl-CN, -SH, $-NH_2$, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, $-NR^{1.1}CN$, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3}-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$, wherein $R^{2.1}$, $R^{2.2}$, and $R^{2.3}$ have the definition described in the context of the present disclosure.

Or, according to the compound represented by formula H or formula G of the present disclosure (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof, when present, R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, CN, NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, $-NR^{1.1}CN$, -CHO, nitro, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $COOR^{2.1}$-C_{3-8} cycloalkyl, $CO\text{-}NR^{2.1}$-C_{3-8} cycloalkyl, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic-C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered

heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$, wherein $R^{2.1}$, $R^{2.2}$, and $R^{2.3}$ have the definitions described in the context of the present disclosure.

Or, according to the compound represented by formula H or formula G of the present disclosure (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof, when present, R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, C_{1-3} alkyl-O-C_{1-3} alkyl-COOH, C_{1-3} alkyl-O-C_{1-3} alkyl-$CONR^{2.1}$, C_{1-3} alkyl-phosphoric acid, C_{1-3} alkyl-O-C(O)-$OR^{2.1}$, C_{1-3} alkyl-O-C(O)-$NR^{2.1}$, C_{1-3} alkyl-O-C(=O)-C_{1-3} alkyl-(O-C_{1-3} alkyl)v, C_{1-3} alkyl-O-C(=O)-C_{1-6} alkyl-$COOR^{2.1}$, C_{1-3} alkyl-N-C(=O)-C_{1-6} alkyl-$COOR^{2.1}$, C_{1-3} alkyl-N-C(=O)-C_{1-6} alkyl-$COOR^{2.1}$, C_{1-3} alkyl-N-C(=O)-N-C_{1-6} alkyl-$COOR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}$, CH_2CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, CN, C_{1-3} alkyl-CN, C_{1-3} alkyl-NH_2, -SH, -NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3} alkyl-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, -$OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$, wherein $R^{2.1}$, $R^{1.2}$, $R^{1.3}$, and v have the definitions described in the context of the present disclosure.

Or, according to the compound represented by formula H or formula G of the present disclosure (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof, when present, R_{31}, R_{32}, R_{33},

R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, and R_{58} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2, wherein each of the above groups may be optionally substituted with 1, 2, or more substituents of OH, CN, C_{1-3} alkyl-CN, -SH, $-NH_2$, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, $-NR^{1.1}CN$, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3} alkyl-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$, wherein $R^{1.1}$, $R^{1.2}$, $R^{2.1}$, and $R^{2.3}$ have the definitions described in the context of the present disclosure.

Or, according to the compound represented by formula H or formula G of the present disclosure (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof, when present, R_c are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, C_{1-6} alkyl-C_{4-10} heterocycloalkyl, C_{1-6} alkyl-C_{4-10} heterocycloalkenyl, C_{1-6} alkyl-C_{6-20} aryl, C_{1-6} alkyl-C_{5-20} heteroaryl, 5- to 20-membered heteroaryl-O-C_{6-20} aryl-, 5- to 20-membered heteroaryl-N-C_{6-20} aryl-, 5- to 20-membered heteroaryl-S-C_{6-20} aryl-, 5- to 20-membered heteroaryl-CH_2-C_{6-20} aryl-, C_{4-10} cycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-fused C_{6-20} aryl-, C_{4-10} cycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl, C_{4-10} cycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-fused 5- to 20-membered heteroaryl-, C_{4-10} cycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-5- to 20-membered heteroaryl-, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, -$C(O)R_{31}$, -$C(O)OR_{32}$, -$OC(O)R_{33}$, -$S(O)_2R_{34}$, -$S(O)_2OR_{35}$, -$OS(O)_2R_{36}$, and -$P(O)(OR_{37})(OR_{38})$, wherein

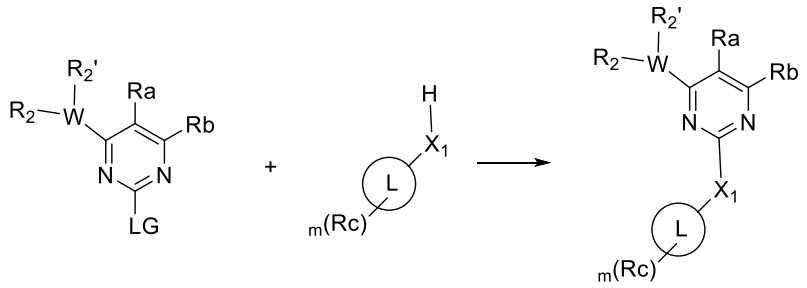
R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, and R_{38} have the definitions described in the context of the present disclosure.

Unless otherwise defined, in the compound according to any one of formulas I to IX in the context of the present disclosure, when some substituents are defined as two linked groups (e.g., in the form of "group 1-group 2", wherein group 1 and group 2 are identical or different), the positions at which the substituents form bonds in the compound according to any one of formulas I to IX are not particularly limited. For example, group 1 may be bonded to a linking position in the compound according to any one of formulas I to IX, or group 2 may be bonded to a linking position in the compound according to any one of formulas I to IX, as long as the aforementioned bonds comply with the valence bond theory. In addition, the position where the two linked groups (e.g., group 1 and group 2) are linked is not particularly limited, as long as the aforementioned linkage complies with the valence bond theory.

For illustrative purposes, groups, such as C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, 5- to 20-membered heteroaryl-C_{1-3} alkyl-$OR^{1.1}$, 3- to 20-membered heterocyclyl-C_{1-6} alkyl, and C_{3-10} cycloalkyl-C_{1-6} alkyl, may represent C_{6-20} aryl-C_{1-6} alkyl-, 5- to 20-membered heteroaryl-C_{1-6} alkyl-, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl)-, 3- to 20-membered heterocyclyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl-C_{1-3} alkyl-$OR^{1.1}$-, 3- to 20-membered heterocyclic-C_{1-6} alkyl-, or C_{3-10} cycloalkyl-C_{1-6} alkyl-, or may also represent -C_{6-20} aryl-C_{1-6} alkyl, -5- to 20-membered heteroaryl-C_{1-6} alkyl, -C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), -3- to 20-membered heterocyclyl-C_{6-20} aryl, -5- to 20-membered heteroaryl-C_{1-3} alkyl-$OR^{1.1}$, -3- to 20-membered heterocyclic-C_{1-6} alkyl, or -C_{3-10} cycloalkyl-C_{1-6} alkyl.

It should be understood that when a chemical bond "-" is added to the left side of group 1 or the right side of group 2 for the above forms of "group 1-group 2", it means that the linking position in the compound according to any one of formulas I to IX has been determined, and the position where a bond is formed in the compound according to any one of formulas I to IX is the corresponding group to which a chemical bond is added.

The present disclosure further provides a preparation method for the compound represented by formula H, or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof, wherein the preparation method comprises reacting a compound of formula A1 with a compound of formula B1 to obtain the compound of formula H:

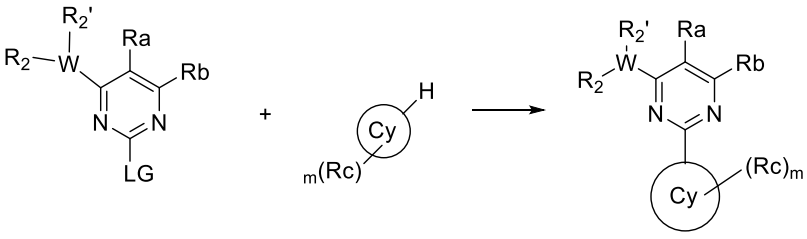


A1 B1 H

wherein LG is a leaving group, such as Cl, Br, or I;

X_1, L, W, R_a, R_b, R_c, R_2, $R_{2'}$, and m are each independently defined as described above.

The present disclosure further provides a preparation method for the compound represented by formula G, or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof, wherein the preparation method comprises reacting a compound of formula A with a compound of formula B to obtain the compound of formula G:



A2 B2 G

and optionally, derivatizing the compound of formula G into the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof;

wherein LG is a leaving group, such as Cl, Br, or I;

Cy, W, R_a, R_b, R_c, R_2, $R_{2'}$, and m are each independently defined as described above.

According to an embodiment of the present disclosure, if desired, the reaction may be performed with a protecting group introduced on the compound of formula A1, a compound of formula A2, the compound of formula B1, or a compound of formula B2. For example, the protecting group may be selected from an amino protecting group, a hydroxyl protecting group, and the like. Suitable protecting groups may be selected from C_{1-40} alkyl and C_{6-20} aryl C_{1-40} alkyl-, e.g., tert-butyl, isopropyl, benzyl, tert-butoxycarbonyl (Boc), 2-biphenyl-2-propoxycarbonyl, benzyloxycarbonyl, fluorenylmethyloxycarbonyl (Fmoc), and trifluoroacetyl.

According to an embodiment of the present disclosure, the preparation method may be performed in the presence of a solvent such as an organic solvent. For example, the organic

solvent may be selected from at least one of the following: alcohols such as methanol, ethanol, isopropanol and *n*-butanol; ethers such as ethyl propyl ether, *n*-butyl ether, anisole, phenetole, cyclohexylmethyl ether, dimethyl ether, diethyl ether, dimethyl glycol, diphenyl ether, dipropyl ether, diisopropyl ether, di-*n*-butyl ether, diisobutyl ether, diisoamyl ether, dimethoxyethane, isopropyl ethyl ether, methyl *tert*-butyl ether, tetrahydrofuran, methyltetrahydrofuran, dioxane, dichlorodiethyl ether, and polyethers of ethylene oxide and/or propylene oxide; aliphatic, cycloaliphatic or aromatic hydrocarbons such as pentane, hexane, heptane, octane, nonane, and those that may be substituted with fluorine and chlorine atoms, such as methylene chloride, dichloromethane, trichloromethane, tetrachloromethane, fluorobenzene, chlorobenzene or dichlorobenzene; cyclohexane, methylcyclohexane, petroleum ether, octane, benzene, toluene, chlorobenzene, bromobenzene, and xylene; and esters such as methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate and dimethyl carbonate, dibutyl carbonate or ethylene carbonate.

The present disclosure further provides a pharmaceutical composition comprising a therapeutically effective amount of at least one of the compound represented by formula H or formula G (e.g., any one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof.

According to an embodiment of the present disclosure, the pharmaceutical composition further comprises one or more pharmaceutically acceptable auxiliary materials.

According to an embodiment of the present disclosure, the pharmaceutical composition may further comprise one or more additional therapeutic agents. The additional therapeutic agent may be selected from therapeutic agents having the same or different targets as the compounds of the present disclosure, e.g., a therapeutic agent for cancer.

The present disclosure further provides use of at least one of the compound represented by formula H or formula G (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof in the preparation of a medicament.

The medicament may be used for preventing or treating a disease.

The present disclosure further provides a method for preventing or treating a disease, comprising administering to a patient in need at least one of the compound represented by formula H or formula G (e.g., one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof.

According to an embodiment of the present disclosure, the disease may be a PDE4B-mediated disease, or a disease mediated at least in part by PDE4.

For example, the disease mediated at least in part by PDE4 is selected from a PDE4-mediated disease, or is selected from a disease mediated by at least one (e.g., 1, 2, 3, or 4) of PDE1, PDE2, PDE3, and PDE5.

For example, the medicament may be used for preventing or treating a disease mediated by PDE4 and at least one (e.g., 1, 2, 3, or 4) selected from PDE1, PDE2, PDE3, and PDE5.

According to an embodiment of the present disclosure, the PDE4 is selected from PDE4A, PDE4B (e.g., PDE4B2), PDE4C, and PDE4D (e.g., PDE4D2).

According to an embodiment of the present disclosure, the PDE1 is selected from PDE1A, PDE1B, and PDE1C.

According to an embodiment of the present disclosure, the PDE2 is selected from PDE2A.

According to an embodiment of the present disclosure, the PDE3 is selected from PDE3A and PDE3B.

According to an embodiment of the present disclosure, the PDE5 is selected from PDE5A.

According to an embodiment of the present disclosure, the disease includes, but is not limited to, inflammatory diseases of the respiratory tract, inflammatory bowel diseases, arthritic diseases, dermatological inflammatory diseases, ocular inflammatory diseases, peripheral or central nervous system diseases, degenerative diseases of the central nervous system, Alzheimer's disease (AD), non-alcoholic steatohepatitis (NASH), idiopathic pulmonary fibrosis (IPF) or pulmonary hypertension associated therewith, chronic obstructive pulmonary disease (COPD) or pulmonary hypertension associated therewith, hepatic fibrosis (HF), renal fibrosis, benign prostatic hyperplasia (BPH), gastroesophageal reflux disease, obstructive sleep apnea, coronary artery disease, or cancer.

According to an embodiment of the present disclosure, the cancer includes, but is not limited to: gastric cancer, bladder cancer, leukemia, bone cancer, brain cancer, breast cancer, central nervous system cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, gallbladder cancer, gastrointestinal cancer, external genitalia cancer, genitourinary cancer, head cancer, kidney cancer, laryngeal cancer, liver cancer, lung cancer, muscular tissue cancer, neck cancer, oral or nasal mucosa cancer, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, splenic cancer, small intestine cancer, colorectal cancer, testicular cancer, and/or thyroid cancer.

According to an embodiment of the present disclosure, since the compound of the present disclosure has a specific tissue distribution and/or a low hERG inhibition effect, the diseases

are preferably selected from those diseases that are particularly advantageous when the compound having a specific tissue distribution and/or a low hERG inhibition effect is used for prevention or treatment.

For example, lesions of the disease (i.e., the affected region) may include the respiratory system, the digestive system, the excretory system, and/or the reproductive system, e.g., the liver, the kidney, and/or the prostate. For this purpose, the medicament may be a targeted drug for the respiratory system, the digestive system, the excretory system, and/or the reproductive system, such as a liver-targeted drug, a kidney-targeted drug, and/or a prostate-targeted drug.

When used as a medicament, the compound of the present disclosure may be administered in the form of a pharmaceutical composition. Those compositions may be manufactured in a manner well known in the pharmaceutical arts and may be administered by a variety of routes depending on whether local or systemic treatment is desired and the region to be treated. The pharmaceutical composition can be administered topically (e.g., by transdermal, dermal, ocular and mucosal routes, including intranasal, vaginal and rectal administration routes), pulmonarily (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; by intratracheal and intranasal routes), orally or parenterally. The parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial (e.g., intrathecal or intracerebroventricular) administration. The pharmaceutical composition may be administered parenterally in a single large dose form, or may be administered by, for example, continuous infusion pump. The pharmaceutical composition and formulation administered topically may include a transdermal patch, an ointment, a lotion, a cream, a gel, a drop, a suppository, a spray, a liquid and a powder. Conventional pharmaceutical carriers, water, powders or oily bases, thickeners, and the like may be necessary or desirable.

In manufacturing the composition of the present disclosure, the active ingredient is typically mixed with an excipient, diluted with an excipient or enclosed within such a carrier as capsules, sachets, paper, or other container forms. When used as a diluent, the excipient may be a solid, semi-solid or liquid substance that serves as a vehicle, a carrier, or a medium for the active ingredient. Thus, the composition may be in the following forms: tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solution formulations, syrups, aerosols (solid or dissolved in a liquid vehicle); ointments, soft and hard gelatin capsules, suppositories, sterile solutions for injection, and sterile packaged powders containing, for example, up to 10% by weight of active compound.

Certain examples of suitable excipients include lactose, glucose, sucrose, sorbitol, mannitol,

starch, gum arabic, calcium phosphate, alginate, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methylcellulose. The preparation may further comprise a lubricant such as talc, magnesium stearate, and mineral oil; a wetting agent; an emulsifier and a suspending agent; a preservative such as methyl benzoate and hydroxypropyl benzoate; a sweetening agent and a flavoring agent. The composition of the present disclosure may be formulated by the methods known in the art so as to provide immediate, sustained, or delayed release of the active ingredient after administration to the patient.

The composition may be formulated in a unit dosage form. Each dose contains about 5-1000 mg, more typically about 100-500 mg, of the active ingredient. The term “unit dosage form” refers to physically discrete single dosage units suitable for use in human patients and other mammals, each unit containing a predetermined amount of active substance mixed with a suitable pharmaceutical excipient that can produce the desired therapeutic effect by calculation. The active compound may be effective in a wide range of doses and is generally administered in a pharmaceutically effective amount. However, it should be understood that the amount of the compound actually administered is usually determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the selected route of administration, the compound actually administered; the age, weight, and response of an individual patient; the severity of the patient’s symptoms and the like.

In manufacturing solid compositions such as tablets, the main active ingredient is mixed with pharmaceutical excipients to form a solid preformulation composition of a homogeneous mixture comprising the compound of the present disclosure. When those preformulation compositions are referred to as homogeneous, it is meant that the active ingredient is generally distributed evenly throughout the composition so that the composition may be readily divided into equally effective unit dosage forms such as tablets, pills and capsules. The solid preformulation is then divided into unit dosage forms of the above type containing, for example, about 0.1 mg to 1000 mg of the active ingredient of the present disclosure.

The tablets or pills of the present disclosure may be coated or compounded to obtain a dosage form affording the advantage of long-acting effect. For example, the tablets or pills contain an inner dosage component and an outer dosage component, the latter being in the form of an envelope of the former. The two components may be separated by an enteric-coated layer which serves to prevent the disintegration in the stomach to allow the inner component to pass through the duodenum entirely or to be delayed in release. A variety of substances may be used for such enteric-coated layers or coatings, including various polymeric acids and mixtures of

polymeric acids and such substances as shellac, cetyl alcohol and cellulose acetate.

Liquid forms for oral administration or injection administration in which the compound and composition of the present disclosure may be incorporated include aqueous solutions, suitable flavoring syrups, aqueous or oil suspensions; and emulsions flavored with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil; as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solution formulations and suspensions in pharmaceutically acceptable aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described above. In certain embodiments, the composition is administered by the oral or nasal inhalation route for local or systemic effect. The composition may be nebulized using an inert gas. The nebulized solution may be inhaled directly from the nebulizing device or the nebulizing device may be connected to a face mask, tent or an intermittent positive pressure ventilator. The solution, suspension, or powder compositions may be administered orally, or nasally by means of a device which delivers the formulation in a suitable manner.

The amount of the compound or composition administered to a patient is not fixed and is dependent on the drug administered, the purpose of the administration such as prevention or treatment; the condition of the patient, the route of administration, etc. In therapeutic applications, the composition may be administered to a patient suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. The effective dosage should be determined based on the state of the disease being treated and the judgment of the attending clinician that depends on factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The composition administered to the patient may be in the form of the pharmaceutical composition described above. These compositions can be sterilized by using conventional sterilization techniques or by filtration. The aqueous solutions may be packaged for use as is, or lyophilized, or the lyophilized formulation is mixed with a sterile aqueous carrier prior to administration. The compound formulation usually has a pH of 3-11, more preferably 5-9, and most preferably 7-8. It should be understood that the use of certain excipients, carriers, or stabilizers described above may result in the formation of a pharmaceutical salt.

The therapeutic dosage of the compound of the present disclosure can be determined, for example, according to: the specific use of the treatment, the route of administration of the compound, the health and condition of the patient, and the judgment of the prescriber. The proportion or concentration of the compound of the present disclosure in the pharmaceutical

composition may vary depending on a variety of factors including the dosage, chemical properties (e.g., hydrophobicity), and the route of administration. For example, the compound of the present disclosure may be provided for parenteral administration by a physiological buffered aqueous solution containing about 0.1-10% w/v of the compound. Certain typical dosage ranges from about 1 μg/kg body weight/day to about 1 g/kg body weight/day. In certain embodiments, the dosage ranges from about 0.01 mg/kg body weight/day to about 100 mg/kg body weight/day. The dosage is likely dependent on such variables as the type and degree of progression of the disease or condition, the general health condition of a particular patient, the relative biological potency of the compound selected, the excipient formulation, and its route of administration. Effective dosage can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

Advantageous effects

The present disclosure provides a novel compound having a pyrimidine fused ring as a novel parent nucleus, a novel side chain, a novel linker, and a novel substituent. The compounds of the present disclosure have excellent PDE4B inhibitory activity, even at the pmol level. The compounds of the present disclosure also have selective PDE4B inhibitory activity, particularly selective inhibitory activity against PDE4B/4D. Some of the compounds also surprisingly have dual-target or multi-target inhibitory activity.

The compounds of the present disclosure can be used to treat respiratory inflammatory diseases, inflammatory bowel diseases, arthritic diseases, dermatological inflammatory diseases, ocular inflammatory diseases, diseases of the peripheral or central nervous system or cancers. In addition, the compounds of the present disclosure also have specific tissue distribution and/or low hERG inhibition effect, and thus have promising application prospects in tissue-targeting drugs and improved tissue toxicity.

Definitions and Description

Unless otherwise stated, the definitions of groups and terms described in the specification and claims of the present application, including definitions thereof as examples, exemplary definitions, preferred definitions, definitions documented in tables, definitions of specific compounds in the examples, and the like, may be arbitrarily combined and incorporated with each other. The definitions of groups and the structures of the compounds in such combinations and incorporations should be construed as being within the scope of the specification and/or the claims of the present application.

Unless otherwise stated, a numerical range set forth in the specification and claims shall be construed as at least including each specific integer value within the range. For example, the

numerical range “1-20” shall be construed as including each integer value in the numerical range “1-10”, i.e., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and each integer value in the numerical range “11-40”, i.e., 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20. Moreover, when certain numerical ranges are described as “a number”, it shall be construed as including both endpoints of the range, each integer within the range, and each decimal within the range. For example, “a number of 0-10” shall be construed as including not only each of integers 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, but also at least the sums of each integer and 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, or 0.9.

It should be understood that when 1, 2, or more are described herein, “more” shall mean an integer greater than 2, e.g., an integer greater than or equal to 3, e.g., 3, 4, 5, 6, 7, 8, 9, or 10.

The term “halogen” refers to fluorine, chlorine, bromine, and iodine.

The term “C_{1-20} alkyl” should be understood to refer to a linear or branched saturated monovalent hydrocarbyl group having 1-20 carbon atoms. For example, “C_{1-10} alkyl” refers to a linear or branched alkyl group having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms and “C_{1-6} alkyl” refers to a linear or branched alkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms. The alkyl is, e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neopentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, 1,2-dimethylbutyl, or the like, or an isomer thereof.

The term “C_{2-20} alkenyl” should be understood to preferably refer to a linear or branched monovalent hydrocarbyl group containing 1, 2, or more double bonds and having 2-20 carbon atoms, preferably “C_{2-10} alkenyl”. “C_{2-10} alkenyl” should be understood to preferably refer to a linear or branched monovalent hydrocarbyl group containing 1, 2, or more double bonds and having 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms, for example, having 2, 3, 4, 5, or 6 carbon atoms (i.e., C_{2-6} alkenyl) or having 2 or 3 carbon atoms (i.e., C_{2-3} alkenyl). It should be understood that in the case that the alkenyl contains more than one double bond, the double bonds can be separated from one another or conjugated. The alkenyl is, for example, ethenyl, allyl, (*E*)-2-methylethenyl, (*Z*)-2-methylethenyl, (*E*)-but-2-enyl, (*Z*)-but-2-enyl, (*E*)-but-1-enyl, (*Z*)-but-1-enyl, pent-4-enyl, (*E*)-pent-3-enyl, (*Z*)-pent-3-enyl, (*E*)-pent-2-enyl, (*Z*)-pent-2-enyl, (*E*)-pent-1-enyl, (*Z*)-pent-1-enyl, hex-5-enyl, (*E*)-hex-4-enyl, (*Z*)-hex-4-enyl, (*E*)-hex-3-enyl, (*Z*)-hex-3-enyl, (*E*)-hex-2-enyl, (*Z*)-hex-2-enyl, (*E*)-hex-1-enyl, (*Z*)-hex-1-enyl, isopropenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (*E*)-1-methylprop-1-enyl, (*Z*)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (*E*)-2-methylbut-2-enyl, (*Z*)-2-methylbut-2-enyl, (*E*)-1-methylbut-2-enyl,

(*Z*)-1-methylbut-2-enyl, (*E*)-3-methylbut-1-enyl, (*Z*)-3-methylbut-1-enyl, (*E*)-2-methylbut-1-enyl, (*Z*)-2-methylbut-1-enyl, (*E*)-1-methylbut-1-enyl, (*Z*)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, or 1-isopropylvinyl.

The term "C_{2-20} alkynyl" should be understood to refer to a linear or branched monovalent hydrocarbyl group containing 1, 2, or more triple bonds and having 2-20 carbon atoms, preferably "C_{2-10} alkynyl". The term "C_{2-10} alkynyl" should be understood to preferably refer to a linear or branched monovalent hydrocarbyl group containing 1, 2, or more triple bonds and having 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms, for example, having 2, 3, 4, 5, or 6 carbon atoms (i.e., "C_{2-6} alkynyl") or having 2 or 3 carbon atoms ("C_{2-3} alkynyl"). The alkynyl is, for example, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-ynyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl. In particular, the alkynyl is ethynyl, prop-1-ynyl, or prop-2-ynyl.

The term "C_{3-20} cycloalkyl" should be understood to refer to a saturated or unsaturated (e.g., partially unsaturated) monovalent monocyclic or bicyclic (e.g., fused, bridged, or spiro) hydrocarbon ring or tricyclic alkane having 3-20 carbon atoms, preferably "C_{3-10} cycloalkyl". The term "C_{3-10} cycloalkyl" should be understood to refer to a saturated monovalent monocyclic or bicyclic (e.g., bridged ring or spiro ring) hydrocarbon ring or tricyclic alkane having 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The C_{3-10} cycloalkyl may be monocyclic hydrocarbyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, or bicyclic hydrocarbyl such as bornyl, indolyl, hexahydroindolyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 2,7-diazaspiro[3,5]nonyl, 2,6-diazaspiro[3,4]octyl, or tricyclic hydrocarbyl such as adamantyl.

It should be understood by those skilled in the art that the term "C_{3-20} cycloalkyl" is not aromatic. Moreover, when the "C_{3-20} cycloalkyl" described above is unsaturated, it may have 1 or more carbon-carbon double bonds and/or 1 or more carbon-carbon triple bonds. When "C_{3-20} cycloalkyl" has a carbon-carbon double bond, it may also be referred to as "C_{3-20}

cycloalkenyl"; when "C_{3-20} cycloalkyl" has a carbon-carbon triple bond, it may also be referred to as "C_{3-20} cycloalkynyl".

Unless otherwise defined, the term "3- to 20-membered heterocyclyl" refers to a saturated or unsaturated non-aromatic ring or ring system; for example, it is a 4-, 5-, 6- or 7-membered monocyclic ring system, a 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic (e.g., fused, bridged, or spiro) ring system or a 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic ring system, and contains at least one, e.g., 1, 2, 3, 4, 5 or more heteroatoms selected from O, S and N, wherein N and S may also be optionally oxidized to various oxidized forms to form nitrogen oxides, -S(O)- or -$S(O)_2$-. Preferably, the heterocyclyl may be selected from "3- to 10-membered heterocyclyl". The term "3- to 10-membered heterocyclyl" refers to a saturated or unsaturated non-aromatic ring or ring system and contains at least one heteroatom selected from O, S, and N. The heterocyclyl may be linked to the rest of the molecule through any one of the carbon atoms or a nitrogen atom (if present). The heterocyclyl may include fused or bridged rings as well as spiro rings. In particular, the heterocyclyl may include, but is not limited to, 4-membered rings such as azetidinyl and oxetanyl; 5-membered rings such as tetrahydrofuranyl, dioxolyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, and pyrrolinyl; or 6-membered rings such as tetrahydropyranyl, piperidyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, and trithianyl; or 7-membered rings such as diazepanyl. Optionally, the heterocyclyl may be benzo-fused. The heterocyclyl may be bicyclic, for example, but is not limited to, a 5,5-membered ring such as a hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl ring, or a 5,6-membered bicyclic ring such as a hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl ring. Heterocyclyl may be partially unsaturated, i.e., it may contain 1, 2, or more double bonds, for example, but not limited to, dihydrofuranyl, dihydropyranyl, 2,5-dihydro-1*H*-pyrrolyl, 4*H*-[1,3,4]thiadiazinyl, 4,5-dihydrooxazolyl or 4*H*-[1,4]thiazinyl, or it may be benzo-fused, for example, but not limited to, dihydroisoquinolyl. When the 3- to 20-membered heterocyclyl is linked to another group to form the compound of the present disclosure, the group may be linked to the carbon atom on the 3- to 20-membered heterocyclyl, or may be linked to the heteroatom on the 3- to 20-membered heterocyclyl. For example, when the 3- to 20-membered heterocyclyl is selected from piperazinyl, it may be a nitrogen atom on piperazinyl that is linked to the group. Alternatively, when the 3- to 20-membered heterocyclyl is selected from piperidyl, it may be the nitrogen atom on piperidyl or the carbon atom in the para position that is linked to the group. For example, the substituted 4- to 10-membered heterocyclyl may be selected from: 1-methylpyrrolidinyl, 1-ethylpyrrolidinyl, 1-cyclopropylpyrrolidinyl, 1-cyclopropylmethylpyrrolidinyl, 5-methyl-4,5-dihydropyridazin-3(2*H*)-onyl, 1-

methylazetidinyl, and 1-methylpiperidinyl.

The term "C_{6-20} aryl" should be understood to preferably refer to an aromatic or partially aromatic monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic hydrocarbon ring having 6-20 carbon atoms, which may be a single aromatic ring or multiple aromatic rings fused together, preferably "C_{6-14} aryl". The term "C_{6-14} aryl" should be understood to preferably refer to an aromatic or partially aromatic monovalent monocyclic, bicyclic, or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms ("C_{6-14} aryl"), in particular a ring having 6 carbon atoms ("C_6 aryl"), such as phenyl or biphenyl, a ring having 9 carbon atoms ("C_9 aryl"), such as indanyl or indenyl, a ring having 10 carbon atoms ("C_{10} aryl"), such as tetrahydronaphthyl, dihydronaphthyl, or naphthyl, a ring having 13 carbon atoms ("C_{13} aryl"), such as fluorenyl, or a ring having 14 carbon atoms ("C_{14} aryl"), such as anthryl. When the C_{6-20} aryl is substituted, it may be monosubstituted or polysubstituted. In addition, the substitution site is not limited, and the substitution may be, for example, ortho-substitution, para-substitution, or meta-substitution.

The term "5- to 20-membered heteroaryl" refers to a monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic aromatic ring system which has 5-20 ring atoms and contains 1-5 heteroatoms independently selected from N, O and S, such as "5- to 14-membered heteroaryl". The term "5- to 14-membered heteroaryl" should be understood to refer to a monovalent monocyclic, bicyclic, or tricyclic aromatic ring system, which has 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 ring atoms, in particular 5, 6, 9, or 10 carbon atoms, contains 1-5, preferably 1-3 heteroatoms independently selected from N, O, and S, and may be benzo-fused in each case. "Heteroaryl" also refers to a group in which a heteroaromatic ring is fused to 1, 2, or more aryl, alicyclic or heterocyclyl rings, wherein the radical or site of linkage is on the heteroaromatic ring. Non-limiting examples of the term heteroaryl include, for example, pyridinyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, 1,2,4-thiadiazolyl, and pyridazinyl; as well as 1-, 2-, 3-, 5-, 6-, 7- or 8-indolizinyl, 1-, 3-, 4-, 5-, 6- or 7-isoindolyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 2-, 3-, 4-, 5-, 6- or 7-indazolyl, 2-, 4-, 5-, 6-, 7- or 8-purinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8- or 9-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 1-, 4-, 5-, 6-, 7- or 8-phthalazinyl, 2-, 3-, 4-, 5- or 6-naphthyridinyl, 2-, 3-, 5-, 6-, 7- or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 6-or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-4aH-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-carbazolylcarbazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8- or 9-carbolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9- or 10-phenanthridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, 1-, 2-, 4-, 5-, 6-, 7-, 8- or 9-pyridinyl, 2-, 3-, 4-, 5-, 6-, 8-, 9- or 10-phenanthrolinyl,

1-, 2-, 3-, 4-, 6-, 7-, 8- or 9-phenazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9- or 10-phenothiazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9- or 10-phenazinyl, 2-, 3-, 4-, 5-, 6- or 1-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-benzisoquinolyl, 2-, 3-, 4- or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10- or 11-7H-pyrazino[2,3-c]carbazolyl, 2-, 3-, 5-, 6- or 7-2H-furo[3,2-b]-pyranyl, 2-, 3-, 4-, 5-, 7- or 8-5H-pyrido[2,3-d]-o-oxazinyl, 1-, 3- or 5-1H-pyrazolo[4,3-d]-thiazolyl, 2-, 4- or 5-1H-imidazo[4,5-d]thiazolyl, 3-, 5- or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5- or 6-imidazo[2,1-b]thiazolyl, 1-, 3-, 6-, 7-, 8- or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10- or 11-4H-pyrido[2,3-c]carbazolyl, 2-, 3-, 6- or 7-imidazo[1,2-b][1,2,4]triazinyl, 7-benzo[b]thienyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 2-, 4-, 5-, 6- or 7-benzimidazolyl, 2-, 4-, 4-, 5-, 6- or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8- or 9-benzoxapinyl, 2-, 4-, 5-, 6-, 7- or 8-benzoazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10- or 11-1H-pyrrolo[1,2-b][2]benzazapinyl. Typical fused heteroaryl groups include, but are not limited to, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 2-, 3-, 4-, 5-, 6- or 7-benzo[b]thienyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 2-, 4-, 5-, 6- or 7-benzimidazolyl, and 2-, 4-, 5-, 6- or 7-benzothiazolyl. When the 5- to 20-membered heteroaryl is linked to another group to form the compound of the present disclosure, the group may be linked to the carbon atom on the 5- to 20-membered heteroaryl ring, or may be linked to the heteroatom on the 5- to 20-membered heteroaryl ring. When the 5- to 20-membered heteroaryl is substituted, it may be monosubstituted or polysubstituted. In addition, the substitution site is not limited. For example, hydrogen linked to the carbon atom on the heteroaryl ring may be substituted, or hydrogen linked to the heteroatom on the heteroaryl ring may be substituted.

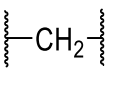
The term “spiro ring” refers to a ring system in which two rings share 1 ring-forming atom.

The term “fused ring” refers to a ring system in which two rings share 2 ring-forming atoms.

The term “bridged ring” refers to a ring system in which two rings share not less than 3 ring-forming atoms.

Unless otherwise stated, the heterocyclyl, 5- to 20-membered heteroaryl, or heteroarylene includes all possible isomeric forms thereof, e.g., position isomers thereof. Thus, for some illustrative non-limiting examples, forms that involving substitutions at or bonding to other groups at 1, 2, or more of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and the like (if present) are included, including pyridin-2-yl, pyridinylene-2-yl, pyridin-3-yl, pyridinylene-3-yl, pyridin-4-yl and pyridinylene-4-yl; thienyl or thienylene, including thien-2-yl, thien-2-ylene, thien-3-yl, and thien-3-ylene; pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl.

The term “oxo (=O)” means that hydrogen or a lone pair of electrons on a non-oxygen atom is

substituted with oxygen; for example,  is oxo-substituted to become , and  is oxo-substituted to become  or .

Definitions of terms herein apply equally to groups containing the term unless otherwise stated. For example, the definition of C_{1-6} alkyl also applies to C_{1-6} alkyloxy, C_{3-8} cycloalkyl-C_{1-6} alkyl-, etc.

In the context of the present disclosure, "-", "--", "---", or "" on a substituent is intended to mark the chemical bond used by the substituent for linkage.

It should be understood by those skilled in the art that the compound represented by formula I may be present in the form of various pharmaceutically acceptable salts. If such compounds have basic centers, they can form acid addition salts; if such compounds have acidic centers, they can form base addition salts; if these compounds comprise both acidic centers (e.g., carboxyl) and basic centers (e.g., amino), they can also form internal salts.

The compound of the present disclosure may be present in the form of a solvate (e.g., hydrate), and the compound of the present disclosure comprises a polar solvent as a structural element of the crystal lattice of the compound, particularly, for example, water, methanol, or ethanol. The amount of the polar solvent, especially water, may be present in a stoichiometric or non-stoichiometric ratio.

The term "pharmaceutically acceptable" as used herein refers to a substance (e.g., carrier or diluent) that does not affect the biological activity or properties of the compound of the present disclosure and is relatively non-toxic, i.e., the substance can be administered to an individual without causing an adverse biological response or interacting in an undesirable manner with any of the components contained in the composition.

It should be understood by those skilled in the art that the compounds disclosed herein may be present in the form of various pharmaceutically acceptable salts. If these compounds have basic centers, they can form acid addition salts; if these compounds have acidic centers, they can form base addition salts; if these compounds comprise both acidic centers (e.g., carboxyl) and basic centers (e.g., amino), they can also form internal salts.

The term "tautomer" refers to functional isomers resulting from the rapid movement of an atom in a molecule between two positions. The compounds disclosed herein may exhibit the tautomerism. A tautomeric compound may be present in two or more interconvertible forms. Prototropic tautomers result from the migration of a covalently bonded hydrogen atom between

two atoms. Tautomers are generally present in an equilibrium form. Efforts to separate a single tautomer usually lead to a mixture, the physicochemical properties of which are consistent with those of the mixture of the compound. The position of the equilibrium depends on the chemical properties of the molecule. For example, in many aliphatic aldehydes and ketones such as acetaldehyde, the keto form predominates; whereas in phenols, the enol form predominates. In the present disclosure, all tautomeric forms of the compounds are included.

According to the molecular structure, the compound of the present disclosure may be chiral and may therefore be present in various enantiomeric forms. These compounds may therefore be present in a racemic or optically active form. The compound of the present disclosure encompasses isomers with each chiral carbon in R or S configuration, or mixtures and racemates thereof. The compound of the present disclosure or the intermediate thereof may be separated into enantiomers by chemical or physical methods well known to those skilled in the art, or used in such form for synthesis. In the case of racemic amines, diastereoisomers are prepared from mixtures by reaction with optically active resolving agents. Examples of suitable resolving agents are optically active acids such as *R*- or *S*-tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitable *N*-protected amino acids (e.g., *N*-benzoylproline or *N*-benzenesulfonylproline), or various optically active camphorsulfonic acids. Enantiomeric resolution by chromatography can be advantageously conducted with the aid of optically active resolving agents, such as dinitrobenzoylphenylglycine, cellulose triacetate or other carbohydrate derivatives or chirally derivatized methacrylate polymers immobilized on silica gel. Suitable eluents for this purpose are mixtures of solvents containing water or alcohol, for example, hexane/isopropanol/acetonitrile. The corresponding stable isomers can be separated according to known methods, such as extraction, filtration, or column chromatography.

"Isotope" means all isotopes of atoms occurring in the compounds of the present disclosure. Isotopes include those atoms having the same atomic number but different mass numbers. Examples of the isotopes suitable for incorporation into the compound of the present disclosure are hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and $^{36}C1$, respectively. The isotopically-labeled compound of the present disclosure can generally be prepared by conventional techniques known to those skilled in the art or by processes similar to those described in the accompanying examples using an appropriate isotopically labeled reagent in place of a non-isotopically labeled reagent. Such a compound has a variety of potential uses, for example, as a standard sample and reagent in the determination of biological activity. In the case of a stable

isotope, this compound has the potential to favorably modify biological, pharmacological or pharmacokinetic properties.

The term "prodrug" can be converted to the compound disclosed herein with biological activity under physiological conditions or by solvolysis. The prodrug disclosed herein is prepared by modifying a functional group in the compound, wherein the modification may be removed by conventional operation or be removed *in vivo* to give the parent compound. The prodrug includes a compound formed by linking a hydroxyl or amino group of the compound disclosed herein to any group. When the prodrug of the compound disclosed herein is administered to a mammalian individual, the prodrug is cleaved to form a free hydroxyl group and a free amino group.

The term "patient" refers to any animal including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, pigs, cattle, sheep, horses, or primates, and most preferably humans.

The term "therapeutically effective amount" refers to the amount of the active compound or drug that causes a biological or medical response that researchers, veterinarians, physicians or other clinicians are looking for in tissues, systems, animals, individuals or humans, including one or more of the following effects: (1) disease prevention: for example, the prevention of a disease, disorder or condition in an individual who is susceptible to the disease, disorder or condition but has not yet experienced or exhibited the pathology or symptoms of the disease; (2) disease inhibition: for example, the inhibition of a disease, disorder or condition in an individual who is experiencing or exhibiting the pathology or symptoms of the disease, disorder or condition (i.e., the prevention of the further development of the pathology and/or symptoms); and (3) disease alleviation: for example, the alleviation of a disease, disorder or condition in an individual who is experiencing or exhibiting the pathology or symptoms of the disease, disorder or condition (i.e., the reverse of the pathology and/or symptoms).

DETAILED DESCRIPTION

The technical solutions of the present disclosure will be further illustrated in detail with reference to the following specific examples. It should be understood that the following examples are merely exemplary illustrations and explanations of the present disclosure, and should not be construed as limiting the protection scope of the present disclosure. All techniques implemented based on the content of the present disclosure described above are encompassed within the protection scope of the present disclosure.

Unless otherwise stated, the starting materials and reagents used in the following examples are all commercially available products or can be manufactured by using known methods.

Abbreviations:

DMF: *N,N*-Dimethylformamide

DCM: dichloromethane

DIEA: *N,N*-Diisopropylethylamine

TEA: triethylamine

PE: petroleum ether

EA: ethyl acetate

MeCN: acetonitrile

Et_2O: diethyl ether

DMSO: dimethyl sulfoxide

EtOAc: ethyl acetate

THF: tetrahydrofuran

TFA: trifluoroacetic acid

MeOH: methanol

EtOH: ethanol

NaH: Sodium hydride

MeI: Iodomethane

EtI: Ethyliodide

HFP: 1,1,1,3,3,3-Hexafluoro-2propanol

DHP: 3,4-Dihydro-2*H*-pyran

PPTS: Pyridinium 4-methylbenzenesulfonate

PPh_3: Triphenylphosphine

DEAD: Diethyl azodicarboxylate

MsCl: Methanesulfonyl chloride

TMSOTf: Trimethylsilyl trifluoromethanesulfonate

m-CPBA: 3-Chloroperoxybenzoic acid

General Methods:

1. Nuclear Magnetic Resonance (NMR) spectra were recorded on a 400 MHz Bruker AVANCE III 500 instrument. Chemical shifts are reported in *ppm* using the deuterated residual solvent as internal standard. Peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplet; q, quartet; m, multiplet; br s, broad singlet.

2. Purity analyses of the samples were performed on a Waters HPLC/Waters MS system.

Chromatographic Conditions 1:

Column: Waters X-Bridge-C18 50mm*4.6mm*3.5μm

Column Temp.: 40 ℃.

Sample Temp.: room temperature

Detection: UV 214 nm, UV 254 nm

Flow Rate: 2 mL/min.

Mobil Phase A: Water (0.05%TFA)

Mobil Phase B: MeCN (0.05%TFA)

Gradient program: B from 5% to 100% for 1.6 min. and hold 100% for 1.4 min.

Chromatographic Conditions 2:

Column: Waters X Brdige C18: 4.6 mm*50 mm*3.5 μm

Column Temp.: 40 ℃.

Sample Temp.: room temperature

Detection: UV 214 nm, UV 254 nm

Flow Rate: 2 mL/min.

Mobil Phase A: Water (0.01mol/L NH_4HCO_3) B: MeCN

Mobil Phase B: MeCN

Gradient program: B from 5% to 100% for 1.6 min and hold 100% for 1.4 min.

3. Preparative HPLC was performed on a Gilson 281.

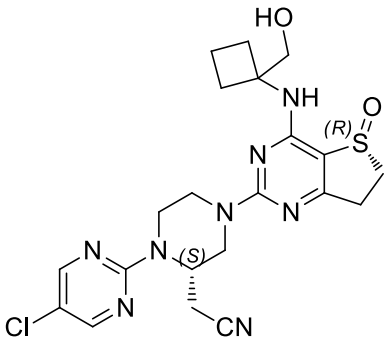
Flow Rate: 20 mL/min.

Column: X-Select10μm 19*250mm column

Wavelength: 254 nM or 214 nM

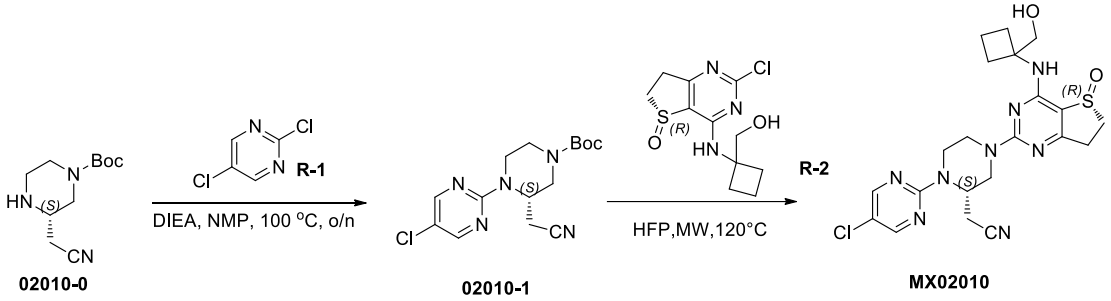
Solvent A water (10 mM NH_4HCO_3) and solvent B Acetonitrile.

Example 1: Synthetic Example



MX02010

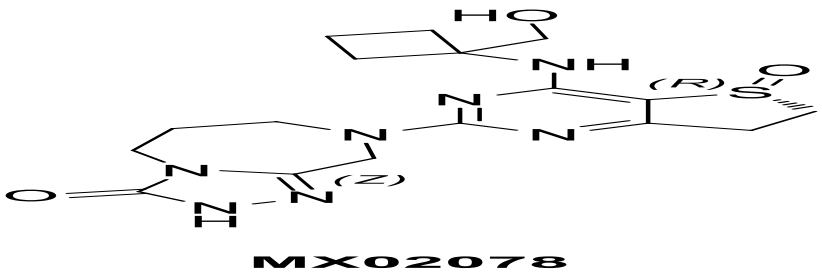
1. Synthetic scheme:



2. Experimental section:

2.1

(*S*)-*tert*-Butyl4-(5-chloropyrimidin-2-yl)-3-(cyanomethyl)piperazine-1-carboxylate (02010-1)



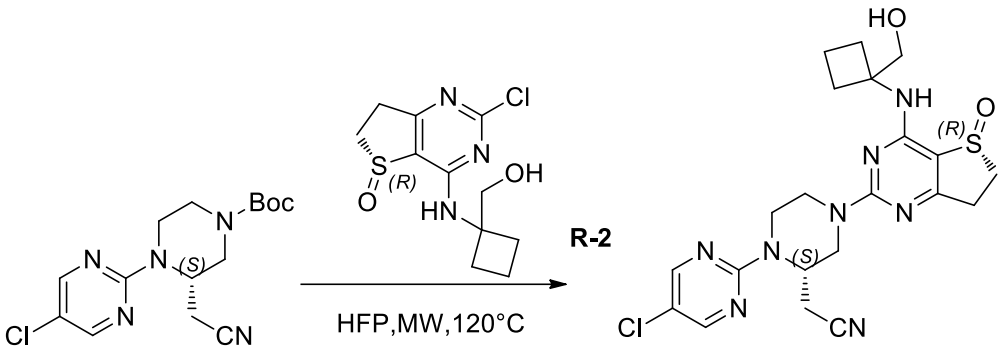
MX02078

To a solution of 2,5-dichloropyrimidine (66 mg, 0.671 mmol) and DIEA (346.4 mg, 2.685 mmol) in NMP (3.0 mL) was added (*S*)-*tert*-butyl 3-(cyanomethyl)piperazine-1-carboxylate (100 mg, 0.671 mmol) at room temperature. The mixture was then stirred at 100 ºC overnight. Water (10 mL) was added and the mixture was extracted with DCM (10 mL*2). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (EA/PE = 0/1~1/4, Silica-CS 12 g, 30 mL/min, silica gel, UV 254) to afford the title compound (46 mg, 30.7% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{15}H_{20}ClN_5O_2]$ $[M-56+H]^+$: 282.1; found: 282.2

2.2

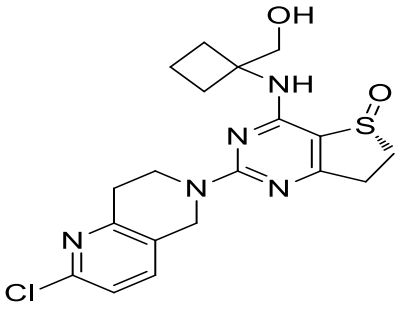
2-((*S*)-1-(5-Chloropyrimidin-2-yl)-4-((*R*)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)piperazin-2-yl)acetonitrile (MX02010)



A solution of (*S*)-*tert*-butyl-4-(5-chloropyrimidin-2-yl)-3- (cyanomethyl)piperazine-1-carboxylate (60 mg, 0.178 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (51 mg, 0.178 mmol) in HFP (3.0 mL) was stirred at 120 °C for 2 hours under microwave condition. Water (10 mL) was added and the mixture was extracted with DCM (10 mL*2). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title compound (16.6 mg, 19.1% yield) as a white solid.

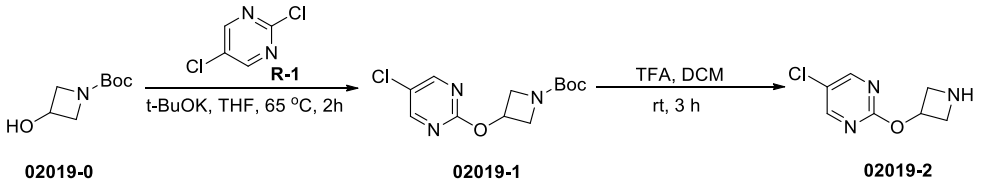
ESI-MS *m/z* calcd for $[C_{21}H_{25}ClN_8O_2S]$ $[M+H]^+$: 489.2; found: 489.0

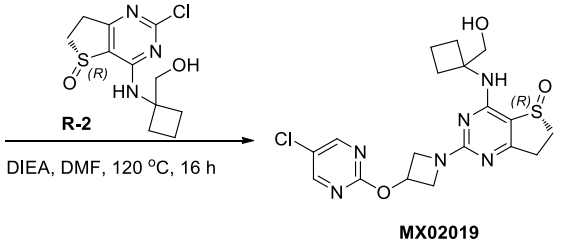
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 2H), 7.49 (s, 1H), 5.11 (s, 1H), 4.82 (t, *J* = 5.2 Hz, 1H),4.61 – 4.47 (m, 3H), 3.76 – 3.68 (m, 2H), 3.46 – 3.35 (m, 1H), 3.30 – 3.16 (m, 2H), 3.10 – 3.05 (m, 1H), 2.98 – 2.80 (m, 4H), 2.46 – 2.20 (m, 5H), 1.82 – 1.71 (m, 2H),



MX02089

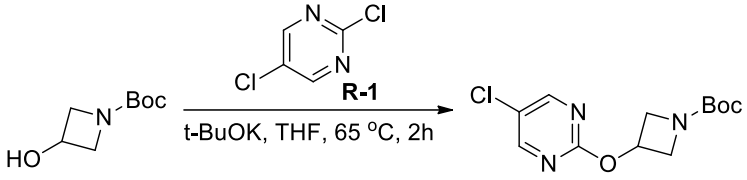
1. Synthetic scheme:





2. Experimental section:

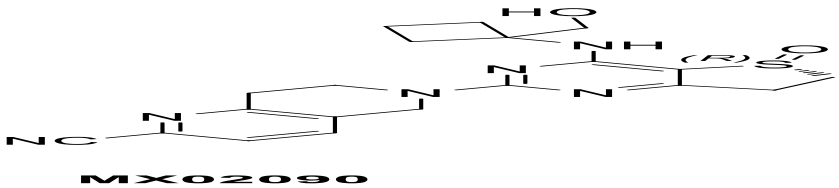
2.1 *tert*-Butyl 3-((5-chloropyrimidin-2-yl)oxy)azetidine-1-carboxylate (02019-1)



To a solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (500 mg, 2.89 mmol) in THF (8 mL) were added 2,5-dichloropyrimidine (430 mg, 2.89 mmol) and *t*-BuOK (647 mg, 5.78 mmol). The resulted mixture was stirred at 65 °C for 2 hours under N_2 atmosphere protection. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water (20 mL) and extracted with EA (50 mL*3). The combined organic layers were washed with saturated saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The resulted crude product was purified by column column chromatography (EA/PE = 0/1~1/1, Silica-CS 20 g, 30 mL/min, silica gel, UV 254) to afford the title product (360 mg, 44% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{12}H_{16}ClN_3O_3]$ $[M-56+H]^+$: 230.1; found: 230.1

2.2 2-(Azetidin-3-yloxy)-5-chloropyrimidine (02019-2)

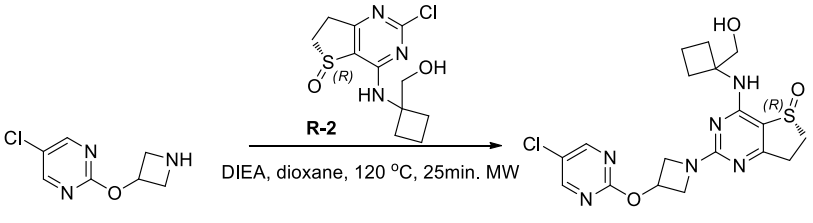


To a solution of *tert*-butyl 3-((5-chloropyrimidin-2-yl)oxy)azetidine-1- carboxylate (360 mg, 1.26 mmol) in DCM (10 mL) was added TFA (1 mL). The resulted mixture was stirred at room temperature for 3 hours under N_2 atmosphere protection. After the completion of the

reaction, the mixture was distilled under reduced pressure to afford the title product (212 mg, 91% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_7H_8ClN_3O]$ $[M+H]^+$: 186.0; found: 186.3

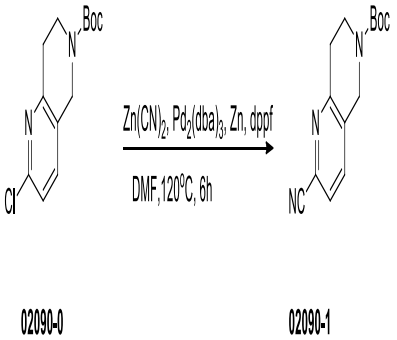
2.3 (*R*)-2-(3-((5-Chloropyrimidin-2-yl)oxy)azetidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02019)



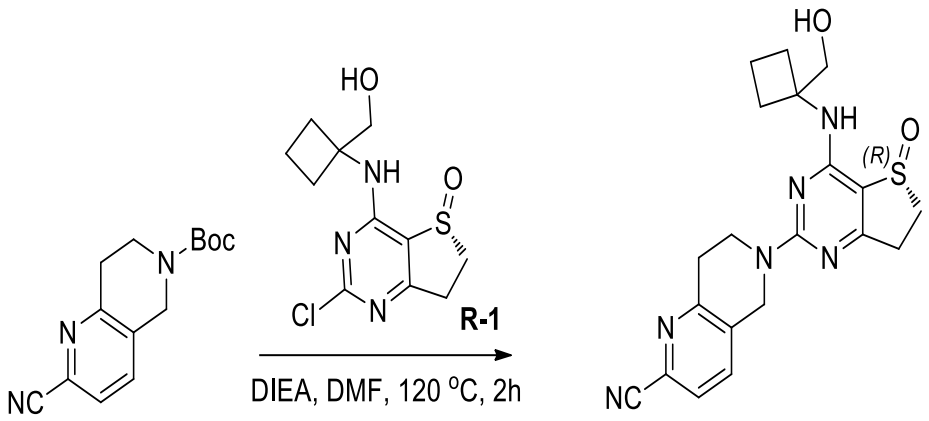
To a solution of 2-(azetidin-3-yloxy)-5-chloropyrimidine (100 mg, 0.54 mmol) in 1,4-dioxane (4 mL) were added (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (155 mg, 0.54 mmol) and DIEA (209 mg, 1.62 mmol). The resulted reaction mixture was stirred at 120 °C for 25 minutes under N_2 atmosphere under microwave condition. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated *in vacuo*. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (36.80 mg, 16% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{18}H_{21}ClN_6O_3S]$ $[M+H]^+$: 437.1; found: 437.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 2H), 7.49 (s, 1H), 5.43 – 5.38 (m, 1H), 4.86 (t, *J* = 5.6 Hz, 1H), 4.42 (dd, *J* = 10.0, 6.4 Hz, 2H), 4.00 (d, *J* = 7.2 Hz, 2H), 3.73 – 3.66 (m, 2H), 3.45 – 3.37 (m, 1H), 3.25 – 3.17 (m, 1H), 2.97 – 2.85 (m, 2H), 2.38 – 2.25 (m, 2H), 2.14 – 2.10 (m, 2H), 1.82 – 1.68 (m, 2H).



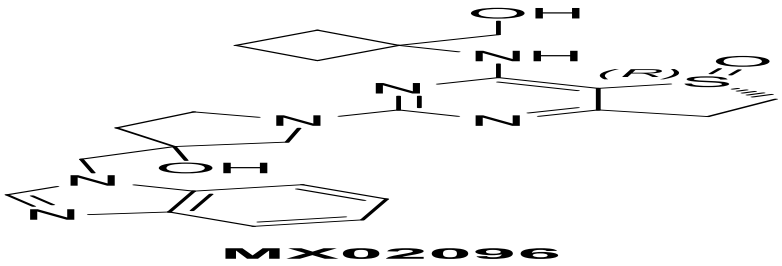
1. Synthetic scheme:



02090-1 **MX02090**

2. Experimental section:

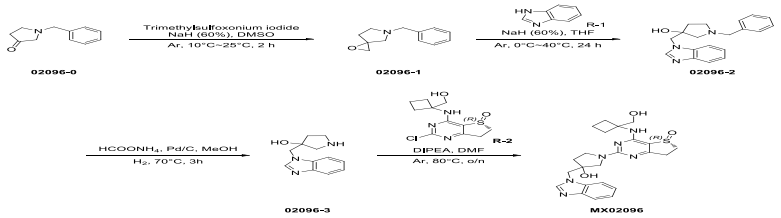
2.1 *tert*-Butyl 5-(5-chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (02020-1)



To a solution of compound *tert*-butyl 2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (100 mg, 0.51 mmol) in DMF (3 mL) were added 2,5-dichloropyrimidine (76 mg, 0.51 mmol) and K_2CO_3 (211 mg, 1.53 mmol). The resulted reaction mixture was stirred at 100 °C for 1 hour under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water (20 mL). and extracted with EA (30 mL*3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/1, Silica-CS 20 g, 30 mL/min, silica gel, UV 254) to afford the title product (140 mg, 90% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{14}H_{19}ClN_4O_2]$ $[M-56+H]^+$: 255.1; found: 255.2

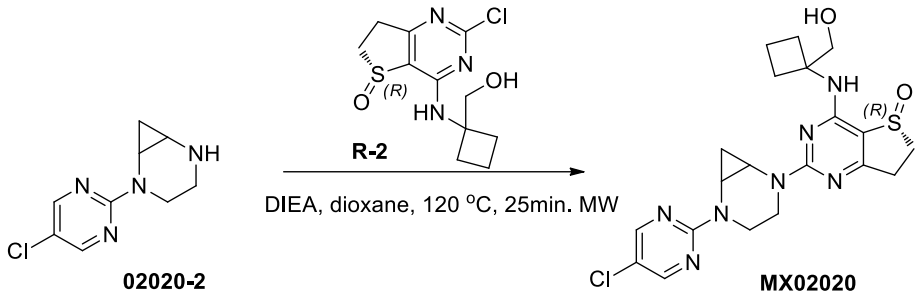
2.2 2-(5-Chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane (02020-2)



To a solution of compound *tert*-butyl 5-(5-chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylate (140 mg, 0.45 mmol) in DCM (5 mL) was added TFA (0.5 mL). The resulted reaction mixture was stirred at room temperature for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the mixture was concentrated to afford the title product (90 mg, 95% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_9H_{11}ClN_4]$ $[M+H]^+$: 211.1; found: 211.3

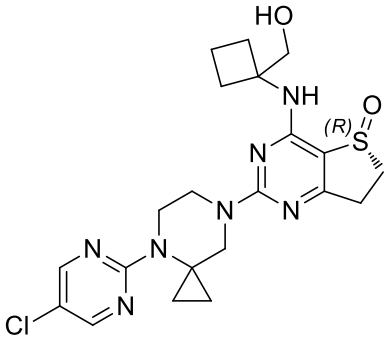
2.3(5*R*)-2-(5-(5-Chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02020)



To a solution of 2-(5-chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane (90 mg, 0.43 mmol) in 1,4-dioxane (4 mL) was added (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (123 mg, 0.43 mmol) and DIEA (165 mg, 1.28 mmol). The resulted reaction mixture was stirred at 120 °C for 25 minutes under N_2 atmosphere under microwave condition. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (19.09 mg, 10% yield) as a white solid.

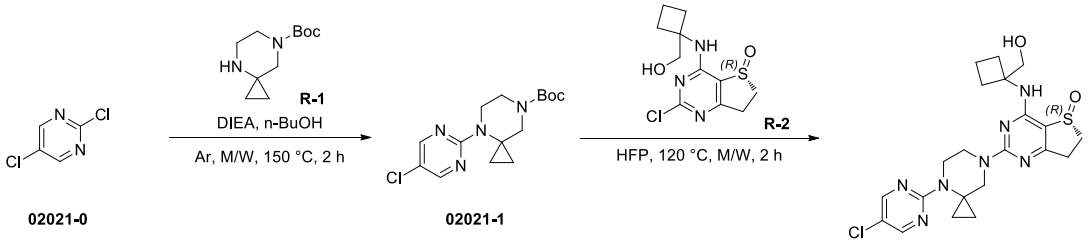
ESI-MS *m/z* calcd for $[C_{20}H_{24}ClN_7O_2S]$ $[M+H]^+$: 462.1; found: 462.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 2H), 7.47– 7.46 (m, 1H), 4.84 (t, J = 6.0 Hz, 1H), 3.98 – 3.53 (m, 7H), 3.45 – 3.41 (m, 2H), 3.26 – 3.19 (m, 1H), 3.00 – 2.96 (m, 1H), 2.91 – 2.86 (m, 1H), 2.39 – 2.33 (m, 2H), 2.18 – 2.17 (m, 2H), 1.83 – 1.70 (m, 2H), 1.16 – 1.15 (m, 1H), 0.42 – 0.36 (m, 1H).



MX02021

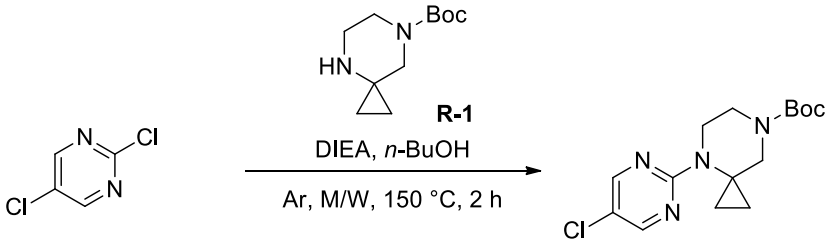
1. Synthetic scheme:



02021-0 **02021-1** **MX02021**

2. Experimental section:

2.1 *tert*-Butyl 4-(5-chloropyrimidin-2-yl)-4,7-diazaspiro[2.5]octane-7-carboxylate (02021-1)

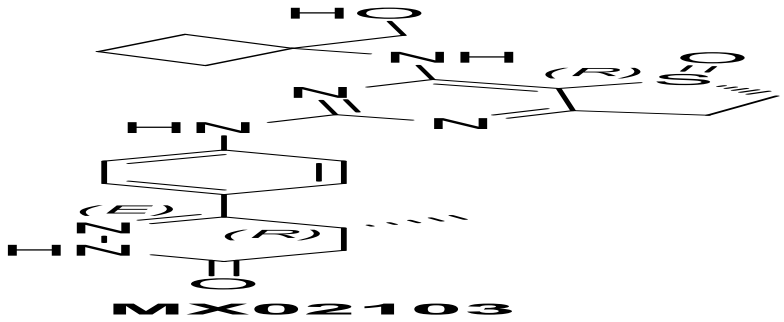


02021-0 **02021-1**

A mixture of 2,5-dichloropyrimidine (200 mg, 1.34 mmol), *tert*-butyl 4,7-diazaspiro[2.5]octane-7-carboxylate (711 mg, 3.35 mmol) and DIEA(1.1 mL, 6.7 mmol) in *n*-BuOH (10 mL) was stirred at 150 ºC for 2 hours under argon under microwave condition. After cooling, the reaction mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0~1/19, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to give the title product (71 mg, 16.3 % yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{15}H_{21}ClN_4O_2]$ $[M-56+H]^+$: 269.1; found: 268.9

2.2(*R*)-2-(4-(5-Chloropyrimidin-2-yl)-4,7-diazaspiro[2.5]octan-7-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02021)

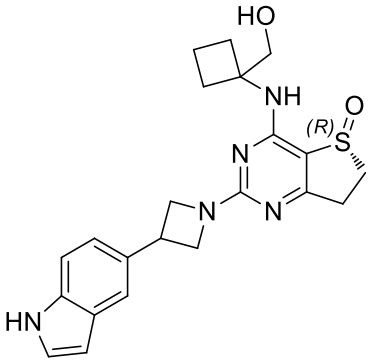


MX02103

A mixture of *tert*-butyl 4-(5-chloropyrimidin-2-yl)-4,7-diazaspiro[2.5]octane-7-carboxylate (44 mg, 0.11 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (32 mg, 0.11 mmol) in HFP (3 mL) was stirred at 120 °C for 2 hours under microwave condition. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by reversed-phase chromatography (MeCN/H_2O =0~12/13, C-18 column, 50 mL/min, UV 214) to give crude product (20 mg) and then the crude prouduct was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (11.48 mg, 17.8 % yield) as a white solid.

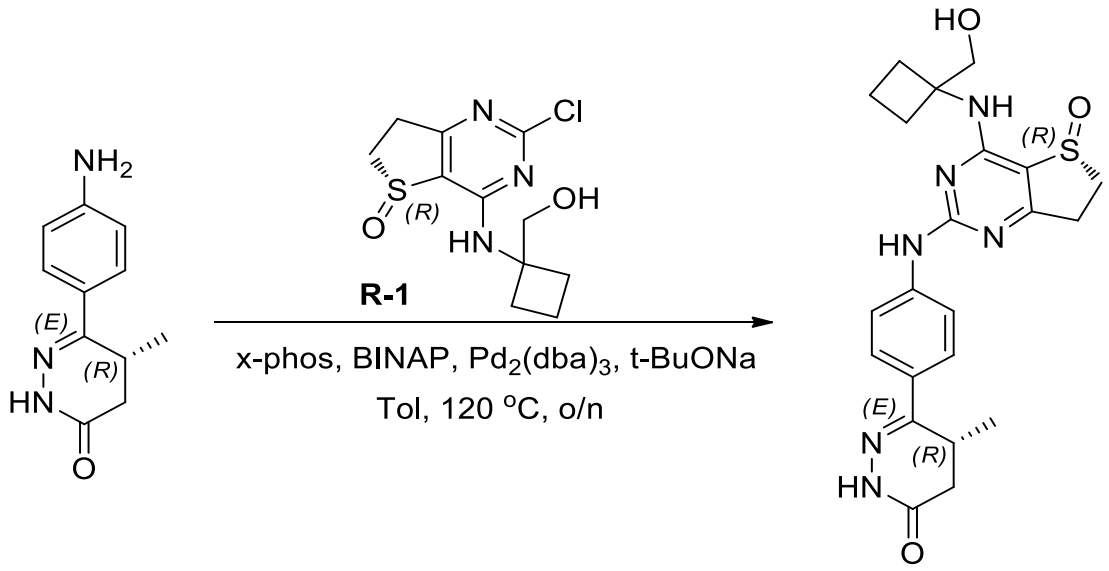
ESI-MS *m/z* calcd for $[C_{21}H_{26}ClN_7O_2S]$ $[M+H]^+$: 476.2; found: 475.8

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 2H), 7.41 – 7.38 (m, 1H), 4.85 (t, *J* =5.6 Hz, 1H), 3.95 – 3.93 (m, 2H), 3.83 – 3.66 (m, 6H), 3.40 – 3.37 (m, 1H), 3.24 – 3.16 (m, 1H), 2.95 – 2.83 (m, 2H), 2.33 – 2.12 (m, 4H), 1.77 – 1.73 (m, 2H), 0.95 – 0.89 (m, 4H).



MX02024

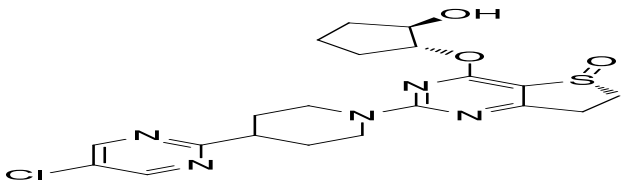
1. Synthetic scheme:



2103-0 **MX02103**

2. Experimental section:

2.1 5-Iodo-1-(triisopropylsilyl)-1*H*-indole (02024-1)



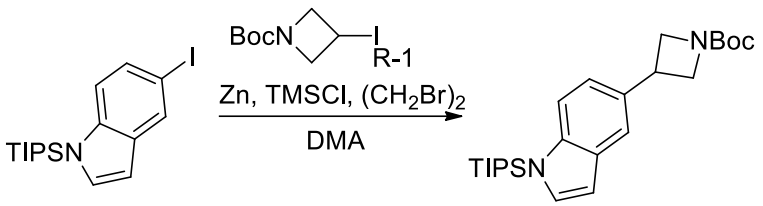
MX02108

A solution of 5-iodo-1*H*-indole (1.7 g, 6.99 mmol) in anhydrous THF (20 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 364 mg, 9.09 mmol) in THF (20 mL) at 0 ºC. The mixture was allowed to slowly warm to room temperature over 30 minutes. Then TIPSCl (1.75g, 9.09 mmol) was added dropwise over 5 minutes. The resulting mixture was slowly warmed to room temperature and stirred until consumption of starting material as monitored by TLC. Once completion, the reaction was quenched at 0 °C with aq. NH_4Cl (20 mL) and extracted with Et_2O (15 mL*3). The combined organic phases was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0~10%, Silica-CS 40 g, 50 mL/min, silica gel, UV 254) to give the title product (2.1 g, 75.17 % yield) as colorless oil.

ESI-MS *m/z* calcd for [$C_{17}H_{26}INSi$]

^{1}H NMR (400 MHz, chloroform-*d*) δ 7.95 (d, *J* = 1.6 Hz, 1H), 7.38 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.20 (d, *J* = 3.2 Hz, 1H), 6.54 (d, *J* = 2.8 Hz, 1H), 1.71 – 1.63 (m, 3H), 1.14 – 1.12 (m, 18H).

2.2 *tert*-Butyl 3-(1-(triisopropylsilyl)-1*H*-indol-5-yl)azetidine-1-carboxylate (02024-2)

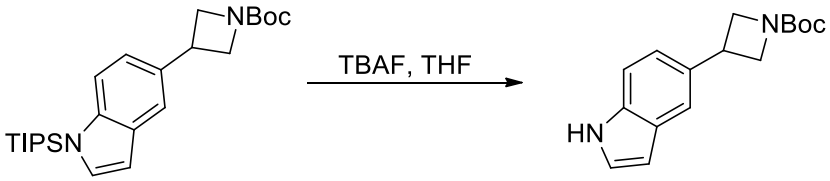


02024-1 **02024-2**

In an inert atmosphere, zinc dust (327 mg, 5.01 mmol) was vigorously stirred in DMA (1.6 mL) and heated to 65°C. Subsequently, TMSCl (65 mg, 0.6 mmol) and dibromoethane (113 mg, 0.6 mmol) were added, then the reaction mixture was stirred for another 30 minutes at 65 °C. *tert*-butyl 3-iodoazetidine-1-carboxylate (851 mg, 3.0 mmol) in DMA (2 mL) was added dropwise to the above prepared solution at 65°C, then the reaction mixture was allowed to cool to room temperature. 5-iodo-1-(triisopropylsilyl)-1*H*-indole (800 mg, 2.0 mmol) in DMA (4 mL) was added to the reaction mixture. Subsequently, $Pd(dppf)Cl_2$ (44 mg, 0.06 mmol) and CuI (23 mg, 0.12 mmol) were added. The reaction mixture was heated to 80 °C for 2 hours, cooled to room temperature and quenched with water (150 mL). Ammonium chloride (2 g) was added, and the reaction mixture was extracted with Et_2O (150 mL*2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated.The crude product was purified by column chromatography (EA/PE = 0~10%, Silica-CS 40 g, 50 mL/min, silica gel, UV 254) to give the title product (0.7 g, 81.52 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{25}H_{40}N_2O_2Si]$ $[M+H]^+$: 429.3; found: 429.2

2.3 *tert*-Butyl 3-(1*H*-indol-5-yl)azetidine-1-carboxylate (02024-3)

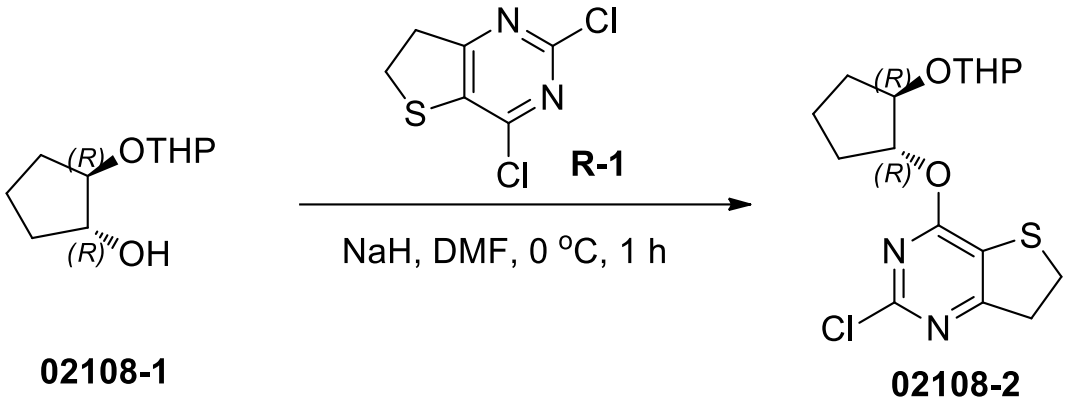


02024-2 **02024-3**

To a solution of *tert*-butyl 3-(1-(triisopropylsilyl)-1H-indol-5-yl)azetidine-1-carboxylate (0.7 g, 1.64 mmol) in THF (10 mL) was added TBAF (1M in THF, 3.27 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. The mixture was quenched with water (30 mL) and extracted with EA (30 mL*2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (EA/PE = 0~30%, Silica-CS 25 g, 30 mL/min, silica gel, UV 254) to give the title product (401 mg, 90.03 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{16}H_{20}N_2O_2]$ $[M-56+H]^+$: 217.2; found: 217.2

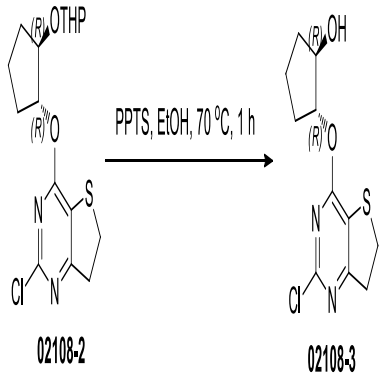
2.4(*R*)-2-(3-(1*H*-Indol-5-yl)azetidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02024)



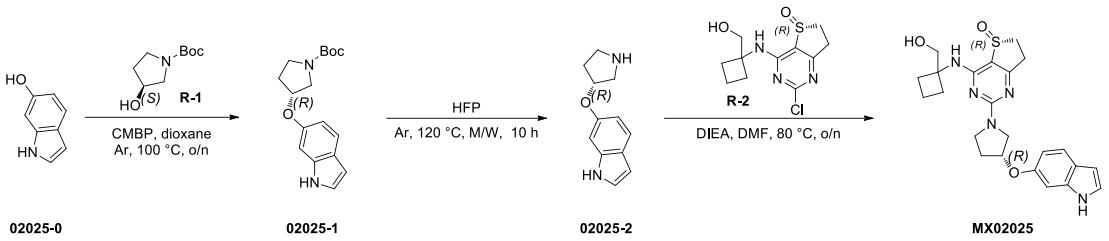
A mixture of *tert*-butyl 3-(1*H*-indol-5-yl)azetidine-1-carboxylate (100 mg, 0.37 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (104 mg, 0.37 mmol) in HFP (3 mL) was heated to 120°C for 2 hours under microwave condition. The mixture was concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title product (58 mg, 37.3 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{22}H_{25}N_5O_2S]$ $[M+H]^+$: 424.2; found: 424.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.50 (s, 1H), 7.41 – 7.37 (m, 2H), 7.32 (t, *J* = 2.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.39 (s, 1H), 4.88 (t, *J* = 5.6 Hz, 1H), 4.46 – 4.42 (m, 2H), 4.03 – 3.94 (m, 3H), 3.71 – 3.70 (m, 2H), 3.44 – 3.38 (m, 1H), 3.26 – 3.18 (m, 1H), 2.98 – 2.85 (m, 2H), 2.39 – 2.31 (m, 2H), 2.15 – 2.10 (m, 2H), 1.80 – 1.70 (m, 2H).

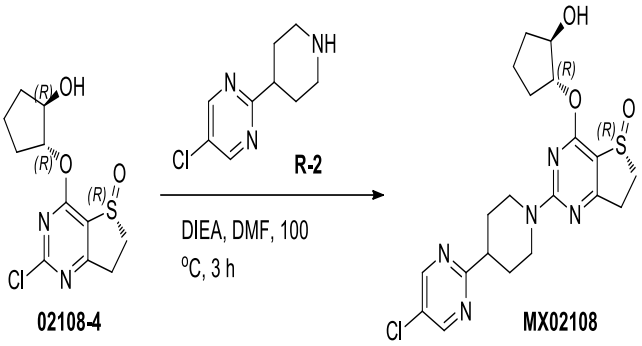


1. Synthetic scheme:



2. Experimental section:

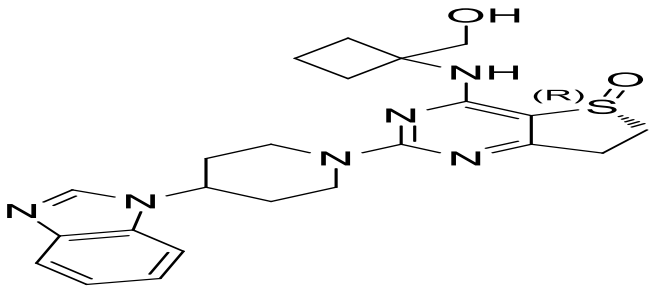
2.1 (*R*)-*tert*-Butyl 3-((1*H*-indol-6-yl)oxy)pyrrolidine-1-carboxylate (02025-1)



To a solution of 1*H*-indol-6-ol (171 mg, 1.284 mmol), (*S*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (200 mg, 1.07 mmol) in dioxane (20 mL) was added CMBP (0.75 mL, 3.21 mmol) and stirred at 100 °C overnight under argon. After cooling, the reaction mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by reversed-phase chromatography ($MeCN/H_2O$ =1/9 ~ 11/9, C-18 column, 50 mL/min, UV 214) to give the title product (322 mg, 99.7 % yield) as brown oil.

ESI-MS *m/z* calcd for $[C_{17}H_{22}N_2O_3]$ $[M-56+H]^+$: 247.2; found: 247.0

2.2 (*R*)-6-(Pyrrolidin-3-yloxy)-1*H*-indole (02025-2)

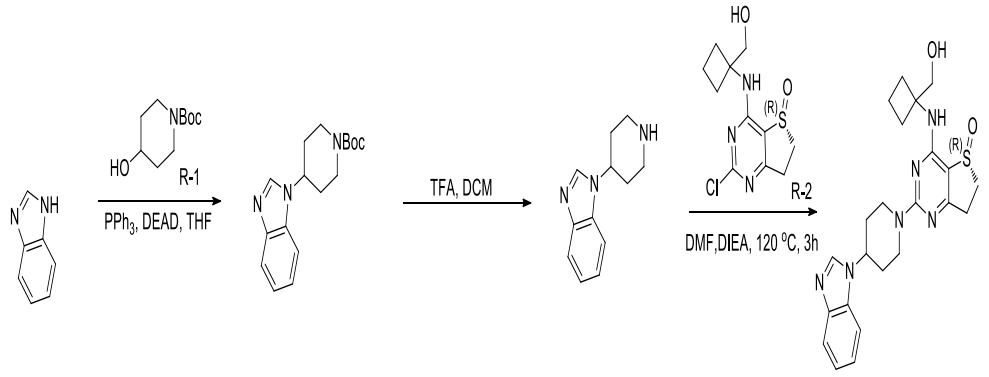


MX02113

A solution of (*R*)-*tert*-butyl 3-((1*H*-indol-6-yl)oxy)pyrrolidine-1-carboxylate (200 mg, 0.66 mmol) in HFP (5 mL) was stirred at 120 °C for 10 hours under argon. After cooling, the mixture was concentrated to give the crude title product (133 mg, 99.4% yield) as brown oil.

ESI-MS *m/z* calcd for $[C_{12}H_{14}N_2O]$ $[M+H]^+$: 203.1; found: 203.2

2.3(*R*)-2-((*R*)-3-((1*H*-Indol-6-yl)oxy)pyrrolidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02025)

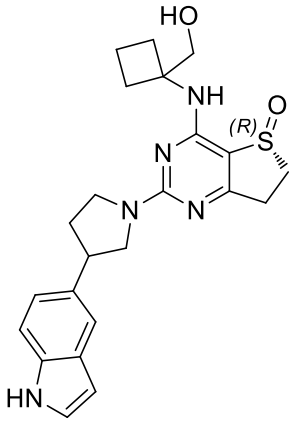


02113-0 02113-1 02113-2 MX02113

To a solution of (*R*)-6-(pyrrolidin-3-yloxy)-1*H*-indole (44 mg, 0.22 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (63 mg, 0.22 mmol) in DMF (10 mL) was added DIEA (0.18 mL, 1.1 mmol). he mixture was then stirred at 80 °C overnight under argon. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (MeOH/DCM = 0~1/9, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give crude product (50 mg) and then the crude prouduct was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (33.02 mg, 33.5 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{23}H_{27}N_5O_3S]$ $[M+H]^+$: 454.2; found: 454.0

^1H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.41 (d, *J* =8.4 Hz, 1H), 7.30 (d, *J* =7.2 Hz, 1H), 7.20 (s, 1H), 6.91 (s, 1H), 6.66 (d, *J* =8.8 Hz, 1H), 6.33 (s, 1H), 5.08 (s, 1H), 4.89 – 4.84 (m, 1H), 3.81 – 3.69 (m, 5H), 3.60 – 3.51 (m, 1H), 3.46 – 3.37 (m, 1H), 3.25 – 3.15 (m, 1H), 2.98 – 2.80 (m, 2H), 2.41 – 2.29 (m, 2H), 2.22 – 2.05 (m, 4H), 1.81 – 1.66 (m, 2H).



MX02026

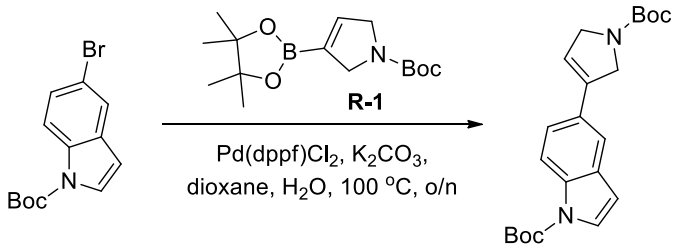
1. Synthetic scheme:



02113-1 **02113-2**

2. Experimental section:

2.1 *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indole-1-carboxylate (02026-1)

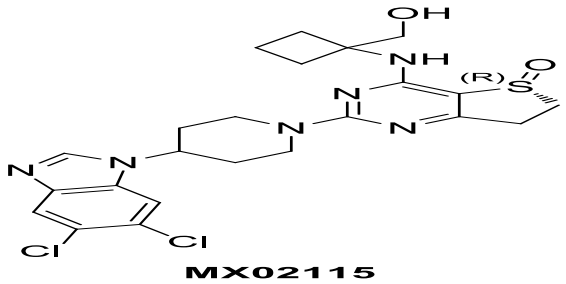


02026-0 **02026-1**

A mixture of *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate (1.0 g, 3.38 mmol), *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (1.0 g, 3.38 mmol), $Pd(dppf)Cl_2$ (247 mg, 0.338 mmol), K_2CO_3 (1.4 g, 10.14 mmol) and H_2O (16 mL) in 1,4-dioxane (80 mL) was stirred at 100 °C overnight under argon. After cooling, the reaction mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0~1/9, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to give the title product (960 mg, 73.9 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{22}H_{28}N_2O_4]$ $[M-56+H]^+$: 329.2; found: 329.2

2.2 *tert*-Butyl 5-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-1*H*-indole-1-carboxylate (02026-2)

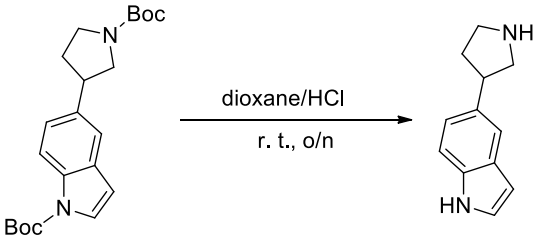


MX02115

To a solution of *tert*-butyl 5-(1-(*tert*-butoxycarbonyl)-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indole-1-carboxylate (300 mg, 0.34 mmol) and DCM (30 mL) in MeOH (75 mL) was added $Pd(OH)_2$ (30 mg) and stirred at room temperature for 12 minutes under hydrogen. After the reaction was accomplished, the mixture was filtered under reduce pressure. The resulting filtrate was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0~1/9, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give the title product (260 mg, 86.2 % yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{22}H_{30}N_2O_4]$ $[M-112+H]^+$: 275.2; found: 275.2

2.3 5-(Pyrrolidin-3-yl)-1*H*-indole (02026-3)

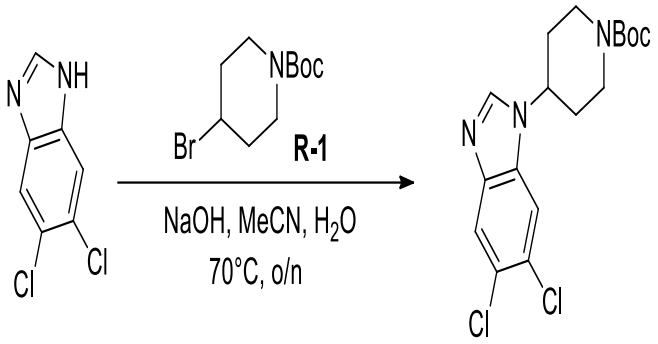


02026-2 02026-3

To a solution of *tert*-butyl 5-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-1*H*-indole-1-carboxylate (248 mg, 0.64 mmol) in 1,4-dioxane (10 mL) was added 4N (HCl)/1,4-dioxane (10 mL) and stirred at room temperature overnight. After the reaction was accomplished, the mixture was evaporated under reduce pressure to remove solvent. The crude product was neutralized by DIPEA (10 mL) and concentrated to give crude title product (119 mg, 99.9 % yield) as a red solid.

ESI-MS *m/z* calcd for $[C_{12}H_{14}N_2]$ $[M+H]^+$: 187.1; found: 187.4

2.4(5*R*)-2-(3-(1*H*-Indol-5-yl)pyrrolidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02026)

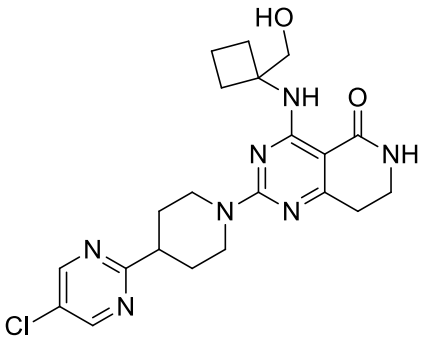


02115-0 02115-1

To a solution of 5-(pyrrolidin-3-yl)-1*H*-indole (130 mg, 0.5 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (144 mg, 0.5 mmol) in1,4-dioxane (10 mL) was added DIEA (0.41 mL, 2.5 mmol) and stirred at 120 °C for 2 hours under microwave condition. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (MeOH/DCM = 0~1/9, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give crude product (50 mg) and then the crude prouduct was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (4.69 mg, 2.1 % yield) as a white solid.

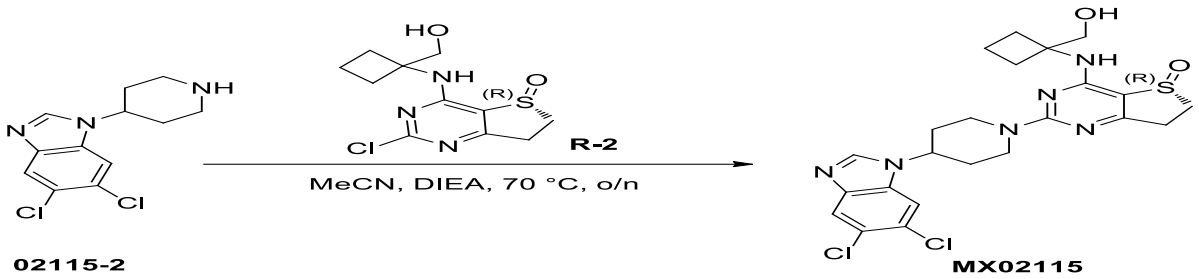
ESI-MS *m/z* calcd for $[C_{23}H_{27}N_5O_2S]$ $[M+H]^+$: 438.2; found: 438.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.46 (d, *J* =4.0 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.05 (d, *J* =8.4 Hz, 1H), 6.37 (s, 1H), 4.90 – 4.84 (m, 1H), 4.05 – 3.95 (m, 1H), 3.82 – 3.67 (m, 3H), 3.56 – 3.39 (m, 4H), 3.24 – 3.17 (m, 1H), 2.95 – 2.86 (m, 2H), 2.46 – 2.27 (m, 3H), 2.18 – 2.04 (m, 3H), 1.79 – 1.66 (m, 2H).



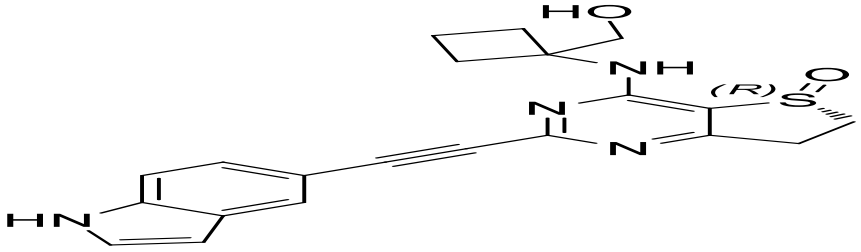
MX02029

1. Synthetic scheme:



2. Experimental section:

2.12-Chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one (02029-1)

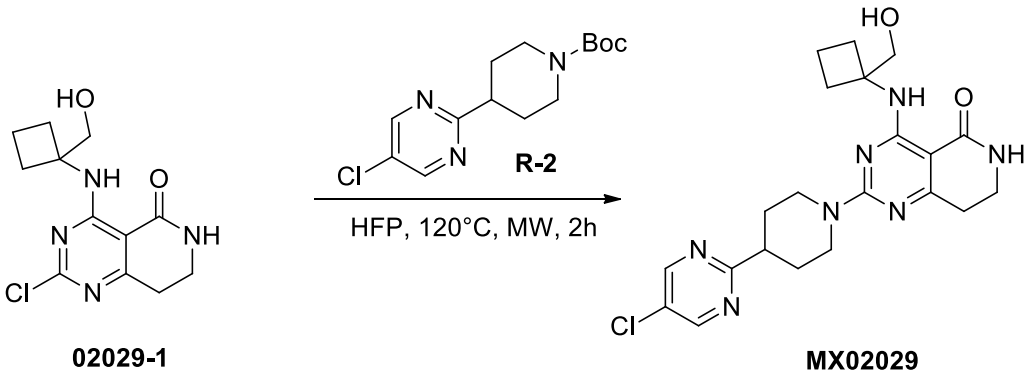


MX02122

To a solution of 2,4-dichloro-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one (23.0 mg, 0.105 mmol) in MeCN (4.0 mL) were added (1-aminocyclobutyl)methanol (11.7 mg, 0.115 mmol) and TEA (1.0 mL). The reaction mixture was stirred at 70 °C overnight. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (MeOH/DCM = 0~1/10, Silica-CS 4 g, 20 mL/min, silica gel, UV 254) to obtain the title product (80% purity, 28.0 mg, 98.0% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{12}H_{15}ClN_4O_2]$ $[M+H]^+$: 283.1; found: 283.1

2.22-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one (MX02029)



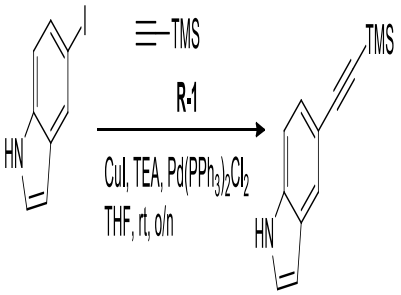
02029-1 **MX02029**

A solution of (2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-7,8-dihydropyrido[4,3-*d*]pyrimidin-5(6*H*)-one (80% purity, 28.0 mg, 0.08 mmol) and

tert-butyl 4-(5-chloropyrimidin-2-yl)piperidine-1-carboxylate (45.0 mg, 0.15 mmol) in HFP (3.0 mL) was stirred at 120 ºC for 2 hours under microwave condition. The reaction mixture was concentrated under reduced pressure and the crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title compound (2.0 mg, 4.55% yield) as a white solid.

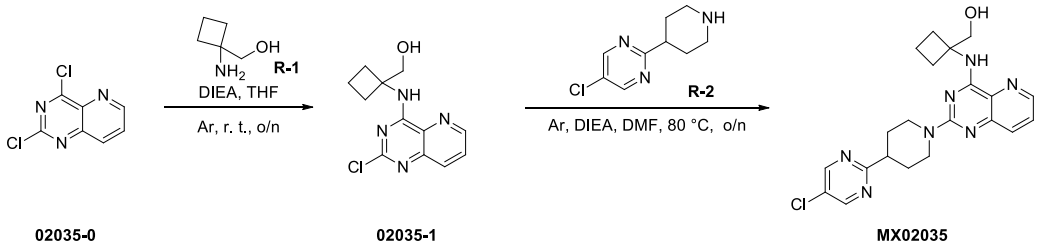
ESI-MS *m/z* calcd for $[C_{21}H_{26}ClN_7O_2]$ $[M+H]^+$: 444.2; found: 444.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.87 (s, 2H), 7.43 (s, 1H), 4.83 (t, *J* = 6.0 Hz, 1H), 4.72 (d, *J* = 10.0 Hz, 2H), 3.69 (d, *J* = 5.2 Hz, 2H), 3.33 – 3.26 (m, 2H), 3.21 – 3.14 (m, 1H), 3.05 – 2.99 (m, 2H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.26 – 2.11 (m, 4H), 1.96 (d, *J* = 10.4 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.67 – 1.59 (m, 2H),



02122-0 02122-1

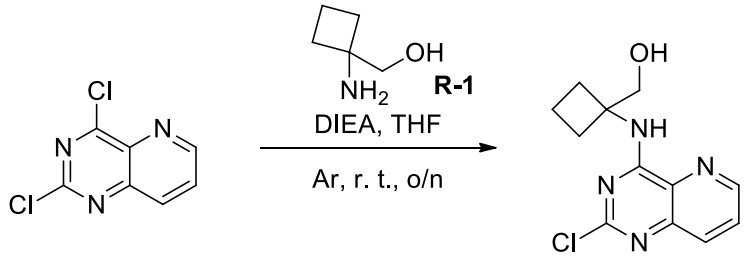
1. Synthetic scheme:



02035-0 02035-1 MX02035

2. Experimental section:

2.1 (1-((2-Chloropyrido[3,2-*d*]pyrimidin-4-yl)amino)cyclobutyl)methanol (02035-1)

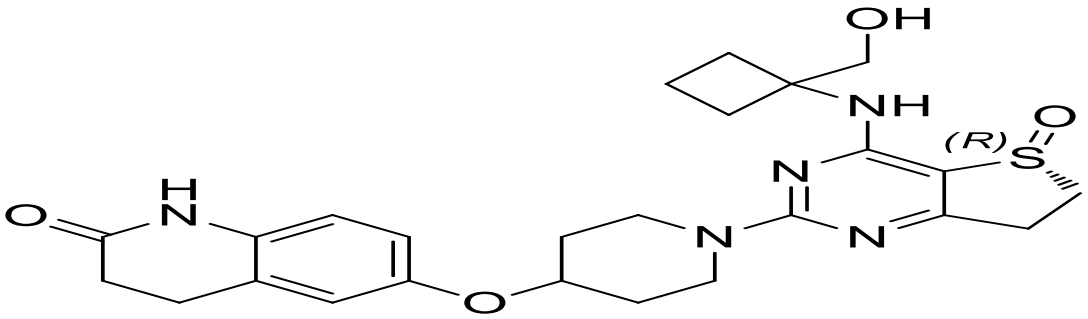


02035-0 02035-1

To a solution of (1-aminocyclobutyl)methanol (50.5 mg, 0.5 mmol) and DIEA (0.1 mL, 0.625 mmol) in THF (5 mL) was added a solution of 2,4-dichloropyrido[3,2-*d*]pyrimidine (100 mg, 0.5 mmol) in THF (15 mL)dropwise over 10 minutes and the resulting mixture was stirring stirred at room temperature overnight under argon. After cooling, the reaction mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0~1/1, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give the title product (105 mg, 79.3 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{12}H_{13}ClN_4O]$ $[M+H]^+$: 265.1; found: 265.1

2.2(1-((2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)pyrido[3,2-*d*]pyrimidin-4-yl)amino)cyclobutyl)methanol (MX02035)

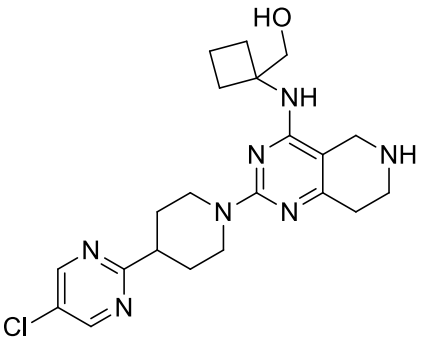


MX02126

To a solution of (1-((2-chloropyrido[3,2-*d*]pyrimidin-4-yl)amino)cyclobutyl)methanol (68 mg, 0.32 mmol) and 5-chloro-2-(piperidin-4-yl)pyrimidine (92 mg, 0.32 mmol) in DMF (20 mL) was added DIEA (0.26 mL, 1.6 mmol) and stirred at 80 ºC overnight under argon. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (MeOH/DCM = 0~1/9, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give crude product (100 mg) and then the crude prouduct was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (73.60 mg, 49.6 % yield) as a white solid.

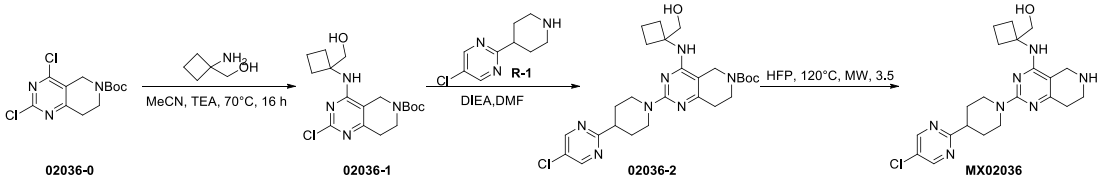
ESI-MS *m/z* calcd for $[C_{21}H_{24}ClN_7O]$ $[M+H]^+$: 426.2; found: 426.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 2H), 8.33 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.65 (dd, *J* =8.4, 1.6 Hz, 1H), 7.57 – 7.53 (m, 2H), 4.99 (t, *J* =5.6 Hz, 1H), 4.83 (d, *J* =12.8 Hz, 2H), 3.78 (d, *J* =5.6 Hz, 2H), 3.22 – 3.16 (m, 1H), 3.10 – 3.04 (m, 2H), 2.64 – 2.56 (m, 2H), 2.18 – 2.11 (m, 2H), 1.99 (d, *J* =10.4 Hz, 2H), 1.88 – 1.65 (m, 4H).



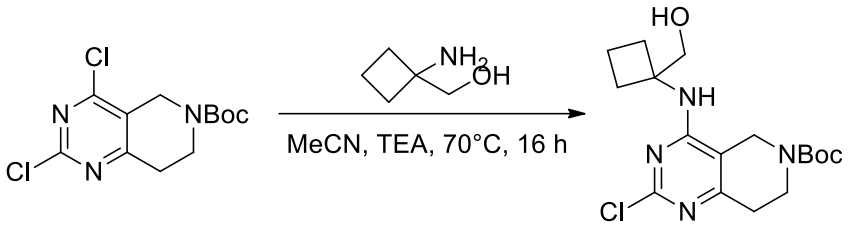
MX02036

1. Synthetic scheme:



2. Experimental section:

2.1 *tert*-Butyl 2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-7,8-dihydropyrido[4,3-*d*] pyrimidine-6(5*H*)-carboxylate (02036-1)

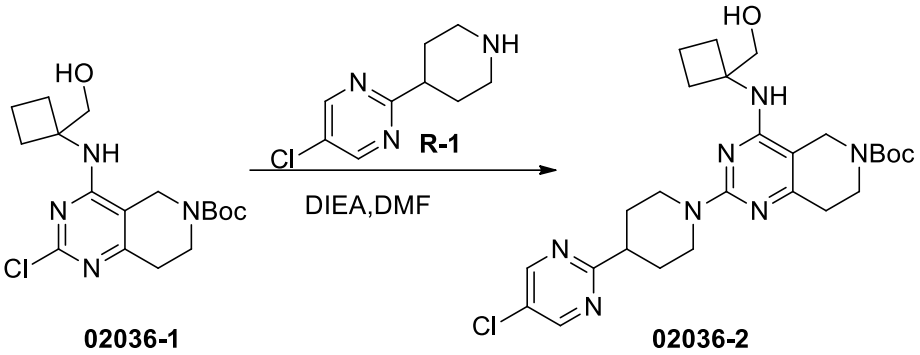


02036-0 **02036-1**

To a solution of *tert*-butyl 2,4-dichloro-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (660 mg, 2.17 mmol) in MeCN (15 mL) were added (1-aminocyclobutyl)methanol (219.5 mg, 2.17 mmol) and TEA (658.7 mg, 6.51 mmol). The reaction mixture was heated to 70°C for 16 hours, cooled to room temperature and concentrated. The crude product was purified by column chromatography (EA/PE = 0~50%, Silica-CS 40 g, 50 mL/min, silica gel, UV 254) to give the title product (441 mg, 55.1% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{17}H_{25}ClN_4O_3]$ $[M+H]^+$: 369.2; found: 369.0

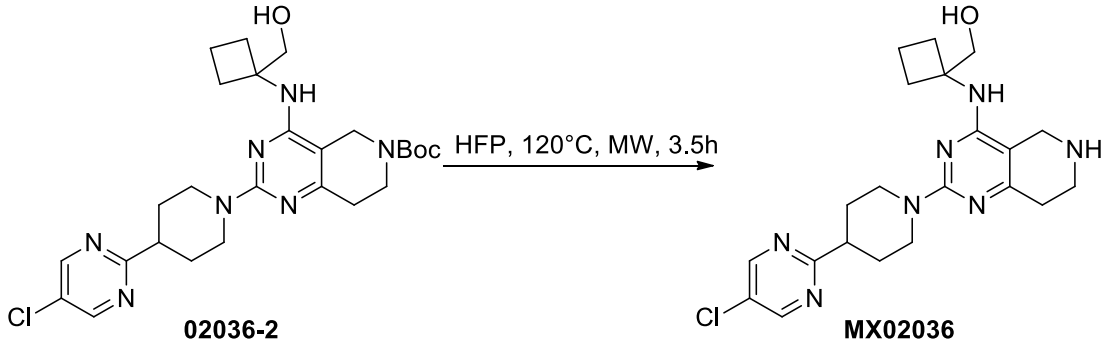
2.2*tert*-Butyl2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-4-((1-(hydroxymethyl) cyclobutyl)amino)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (02036-2)



To a solution of *tert*-butyl 2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5*H*)-carboxylate (441 mg, 1.20 mmol) in DMF (15 mL) were added 5-chloro-2-(piperidin-4-yl)pyrimidine (378 mg, 1.91 mmol) and DIEA (309 mg, 2.39 mmol). The reaction mixture was heated to 120 °C for 16 hours, cooled to room temperature and concentrated. The crude product was purified by column chromatography (MeOH/DCM = 0~10%, Silica-CS 25 g, 30 mL/min, silica gel, UV 254) to give the title product (101 mg, 15.9% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{26}H_{36}ClN_7O_3]$ $[M+H]^+$: 530.3; found: 530.0

2.3(1-((2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)amino)cyclobutyl)methanol (MX02036)

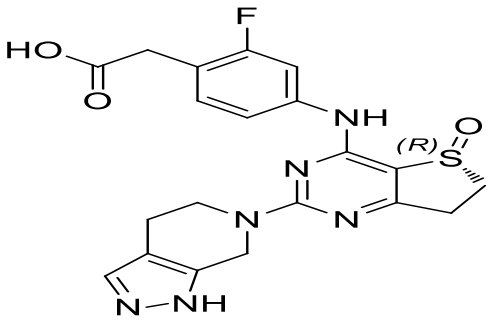


A solution of *tert*-Butyl 2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-4-((1-(hydroxymethyl) cyclobutyl)amino)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (20 mg, 0.04 mmol) in HFP (3.0 mL) was stirred at 120 °C for 3.5 hours under microwave condition.The mixture was concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title product (3.6 mg, 18.0 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{21}H_{28}ClN_7O]$ $[M+H]^+$: 430.2; found: 430.0

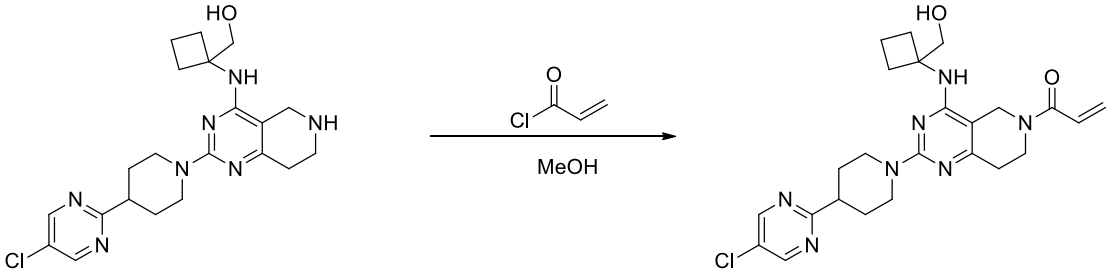
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 2H), 5.83 (s, 1H), 4.78 (t, *J* = 5.6 Hz, 1H), 4.61 – 4.58 (m, 2H), 3.70 (d, *J* = 5.6 Hz, 2H), 3.43 (s, 2H), 3.12 – 3.07 (m, 1H), 2.90 – 2.85 (m, 4H), 2.36 – 2.34 (m, 2H), 2.25 – 2.10 (m, 5H), 1.88 – 1.85 (m, 2H), 1.77 – 1.74 (m, 2H), 1.63 – 1.59

(m, 2H).



MX02128

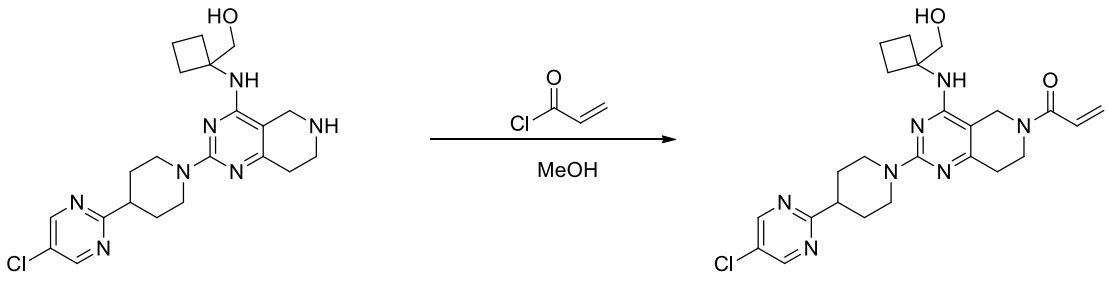
1. Synthetic scheme:



MX02036 MX02037

2. Experimental section:

2.11-(2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-7,8-dihydropyrido[4,3-*d*]pyrimidin-6(5*H*)-yl)prop-2-en-1-one (MX02037)

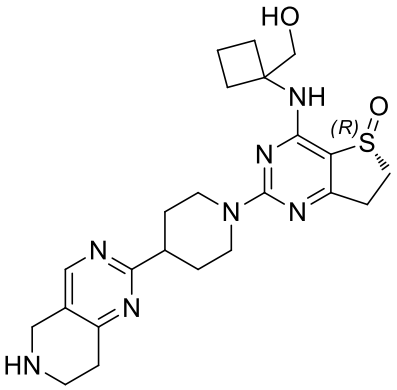


MX02036 MX02037

To a solution of (1-((2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)amino)cyclobutyl)methanol (0.189 mmol, crude) in MeOH (5 mL) was added acryloyl chloride (171 mg, 1.89 mmol). The mixture was stirred at room temperature for 16 hours. The mixture was concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title product (3.20 mg, 3.5 % yield) as a white solid.

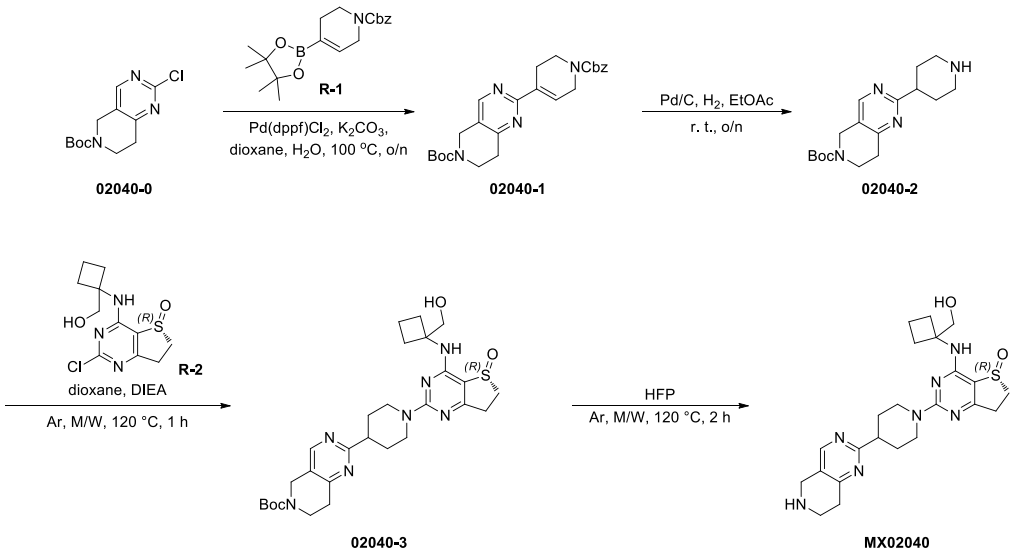
ESI-MS *m/z* calcd for $[C_{24}H_{30}ClN_7O_2]$ $[M+H]^+$: 484.2; found: 484.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 2H), 6.99 – 6.86 (m, 1H), 6.34 (d, *J* = 11.6 Hz, 1H), 6.17 (dd, *J* = 28.0, 16.0 Hz, 1H), 5.74 (dd, *J* = 24.8, 11.2 Hz, 1H), 4.78 – 4.73 (m, 1H), 4.61 (d, *J* = 12.8 Hz, 2H), 4.34 (d, *J* = 14.4 Hz, 2H), 3.75 – 3.72 (m, 4H), 3.14 – 3.09 (m, 1H), 2.90 (t, *J* = 12.0 Hz, 2H), 2.59 – 2.57 (m, 1H), 2.47 – 2.45 (m, 1H), 2.33 -2.17 (m, 4H), 1.89 – 1.73 (m, 4H), 1.64 -1.56 (m, 2H).



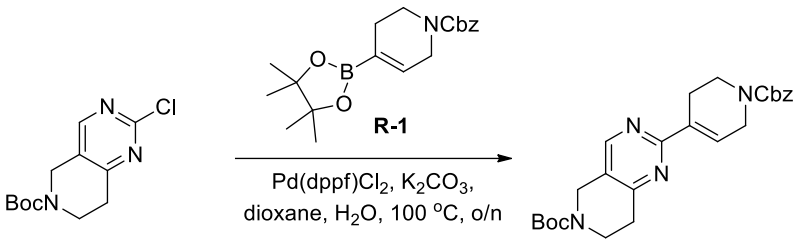
MX02040

1. Synthetic scheme:



2. Experimental section:

2.1*tert*-Butyl-2-(1-((benzyloxy)carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (02040-1)

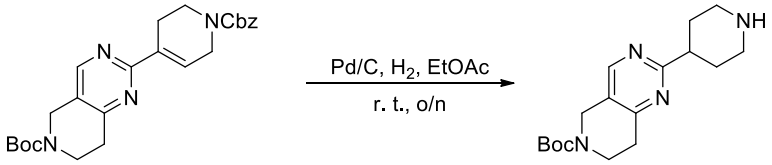


02040-0 02040-1

A mixture of *tert*-butyl 2-chloro-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (300 mg, 1.11 mmol), benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (381 mg, 1.11 mmol), $Pd(dppf)Cl_2$ (81 mg, 0.111 mmol), K_2CO_3 (460 mg, 3.33 mmol) and H_2O (0.8 mL) in 1,4-dioxane (4 mL) was stirred at 100 °C overnight under argon. After cooling, the reaction mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0~1/3, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to give the title product (501 mg, 99.9 % yield) as yellow oil.

ESI-MS *m/z* calcd for $[C_{25}H_{30}N_4O_4]$ $[M-56+H]^+$: 451.2; found: 451.3

2.2*tert*-Butyl-2-(piperidin-4-yl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylatee (02040-2)

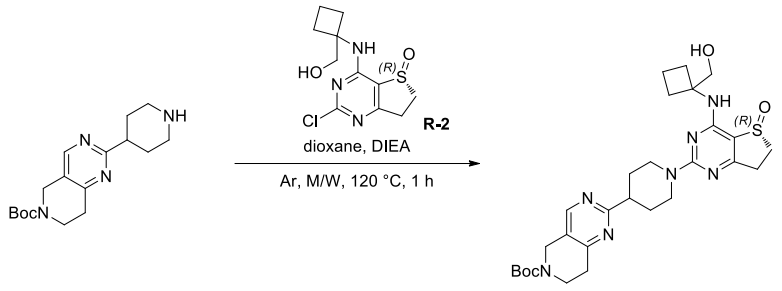


02040-1 02040-2

To a solution of *tert*-butyl 2-(1-((benzyloxy)carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (393 mg, 0.87 mmol) in EA(30 mL) was added Pd/C (80 mg) and stirred at room temperature overnight under hydrogen. After the reaction was accomplished, the mixture was filtered under reduce pressure. The resulting filtrate was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0~1/3, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to give the title product (277 mg, 99.7 % yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{17}H_{26}N_4O_2]$ $[M+H]^+$: 319.2; found: 319.2

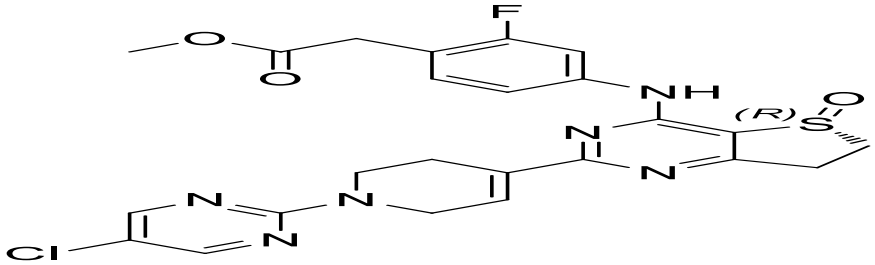
2.3(*R*)-*tert*-Butyl-2-(1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)piperidin-4-yl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (02040-3)



To a solution of *tert*-butyl 2-(piperidin-4-yl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (277 mg, 0.87 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (280 mg, 0.87 mmol) in dioxane (10 mL) was added DIEA (0.43 mL, 2.61 mmol) and the mixture was stirred at 120 ºC for 1 hour under argon under microwave condition. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (MeOH/DCM = 0~1/9, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give the title product (495 mg, 99.9 % yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{28}H_{39}N_7O_4S]$ $[M+H]^+$: 570.3; found: 569.8

2.4(*R*)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(4-(5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-2-yl)piperidin-1-yl)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02040)



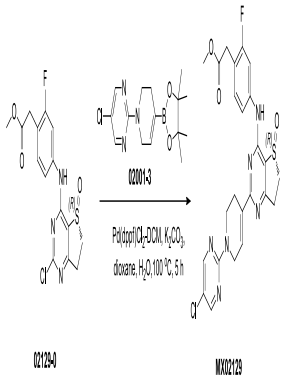
MX02129

A solution of (*R*)-*tert*-butyl 2-(1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)piperidin-4-yl)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5*H*)-carboxylate (150 mg, 0.26 mmol) in HFP (10 mL) was stirred at 120 ºC for 2 hours under argon. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (49.00 mg, 39.6 % yield) as a white solid.

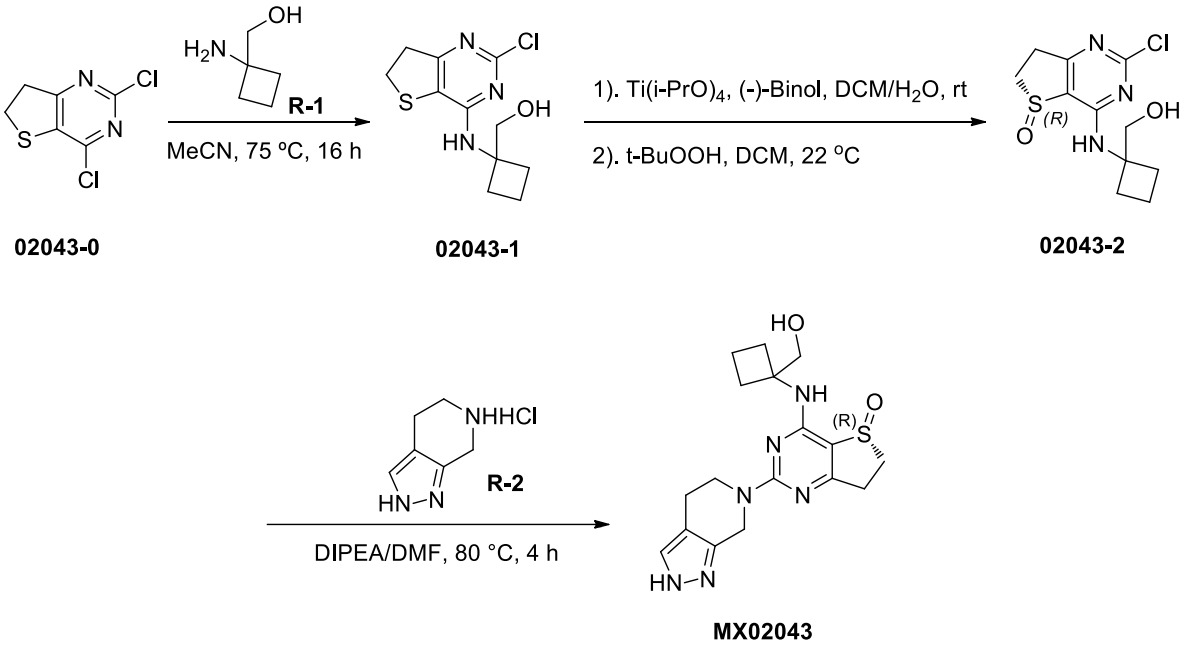
ESI-MS *m/z* calcd for $[C_{23}H_{31}N_7O_2S]$ $[M+H]^+$: 470.2; found: 470.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.36 (s, 1H), 4.85 (t, *J* =5.6 Hz, 1H), 4.71 (d, *J* =12.4 Hz, 2H), 3.79 (s, 2H), 3.73 – 3.71 (m, 2H), 3.45 – 3.37 (m, 1H), 3.24 – 3.17 (m,

1H), 3.09 – 2.83 (m, 8H), 2.69 (t, *J* =6.0 Hz, 2H), 2.39 – 2.25 (m, 2H), 2.18 – 2.12 (m, 2H), 1.91 – 1.88 (m, 2H), 1.79 – 1.73 (m, 2H), 1.65 – 1.61 (m, 2H).

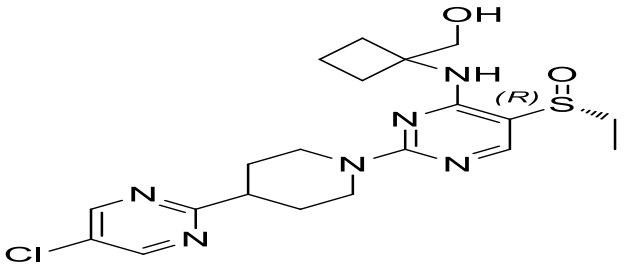


1. Synthetic scheme:



2. Experimental section:

2.1(1-((2-Chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)cyclobutyl)methanol (02043-1)



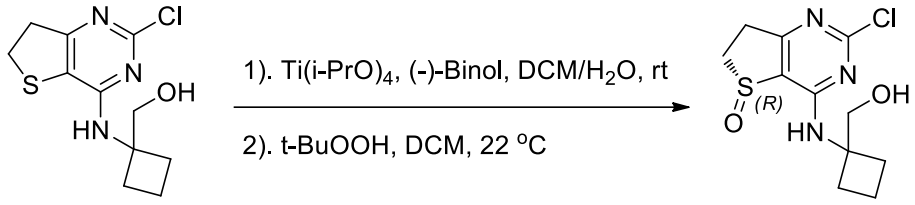
MX02137

To a solution of 2,4-dichloro-6,7-dihydrothieno[3,2-*d*]pyrimidine (6.641 g, 32.07 mmol) in MeCN (50.0 mL)

were added (1-aminocyclobutyl) methanol (3.244 g, 32.07 mmol) and TEA (20.0 mL). The reaction mixture was stirred at 75 °C for 16 hours. The mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (EA/DCM = 0~60%, Silica-CS 120 g, 50 mL/min, silica gel, UV 254) to obtain the title product (4.01 g, 46.1% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{11}H_{14}ClN_3OS]$ $[M+H]^+$: 272.1; found: 272.1

2.2(*R*)-2-Chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (02043-2)



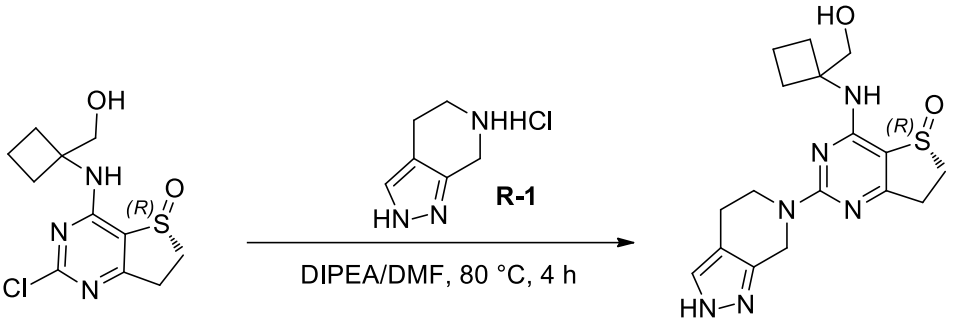
02043-1 **02043-2**

To a solution of (1-((2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)cyclobutyl)methanol (3.5 g, 12.88 mmol) and S(-)-Binol (369.0 mg, 1.288 mmol) in DCM (60 mL) were added $Ti(i\text{-}PrO)_4$ (182.0 mg 0.64 mmol) and H_2O (232.0 mg, 12.88 mmol) . The mixture was stirred for 1 hour at room temperature. *t*-BuOOH (70% in water) (2.0 g, 14.17 mmol) was added at once, then the mixture was stirred for 2 hours at room temperature. Water (50 mL) was added and the mixture was extracted with DCM (60 mL*3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (DCM/MeOH = 1/0~10/1, Silica-CS 80 g, 50 mL/min, silica gel, UV 254) to give the title product (3.50 g, 94.6% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{11}H_{14}ClN_3O_2S]$ $[M+H]^+$: 288.0; found: 288.0

^1H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 4.89 (t, J = 5.6 Hz, 1H), 3.74 – 3.66 (m, 2H), 3.61 – 3.52 (m, 1H), 3.38 – 3.30 (m, 1H), 3.16 – 3.12 (m, 1H), 3.05 – 2.99 (m, 1H), 2.32 – 2.17 (m, 4H), 1.81 – 1.71 (m, 2H).

2.3(*R*)-2-(4,5-Dihydro-2*H*-pyrazolo[3,4-*c*]pyridin-6(7*H*)-yl)-4-((1-(hydroxymethyl) cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02043)

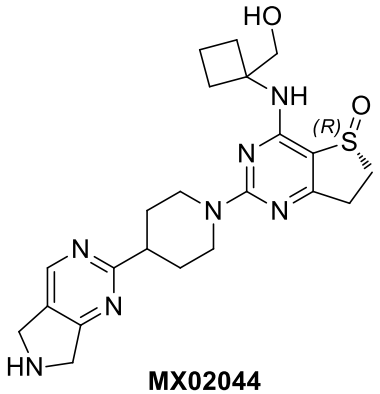


02043-2 **MX02043**

To a solution of (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (57.0 mg, 0.2 mmol) in DMF (5.0 mL) were added 4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*c*]pyridine hydrochloride (38.0 mg, 0.24 mmol) and DIEA (1.5 mL). The reaction mixture was stirred for 4 hours at 80 °C. The reaction mixture was concentrated under reduced pressure and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (20.0mg, 26.9% yield) as a white solid.

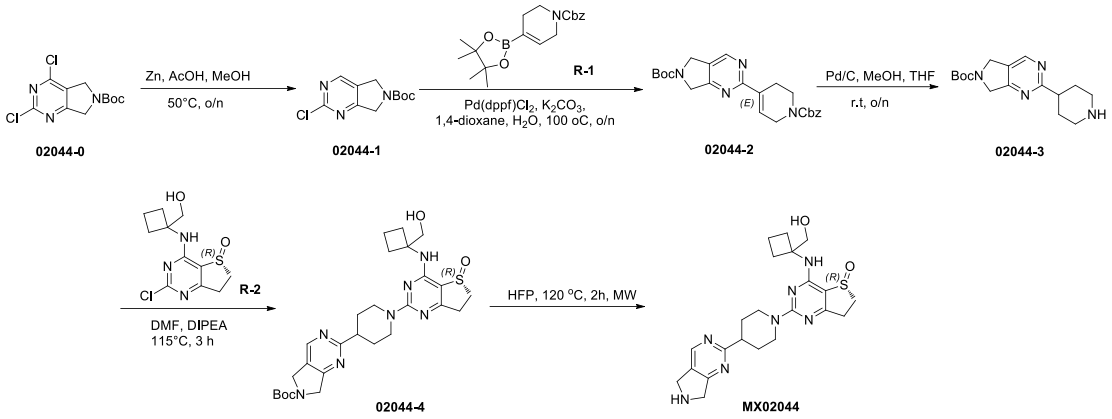
ESI-MS *m/z* calcd for $[C_{17}H_{22}N_6O_2S]$ $[M+H]^+$: 375.2; found: 375.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H), 7.47 (s, 1H), 7.41 (s, 1H), 4.88 – 4.83 (m, 3H), 3.96 (br, 2H), 3.78 – 3.71 (m, 2H), 3.46 – 3.38 (m, 1H), 3.24 – 3.16 (m, 1H), 2.94 (dd, *J* = 16.8, 8.0 Hz, 1H), 2.86 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.67 – 2.61 (m, 2H), 2.40 – 2.27 (m, 2H), 2.21 – 2.17 (m, 2H), 1.82 – 1.74 (m, 2H).



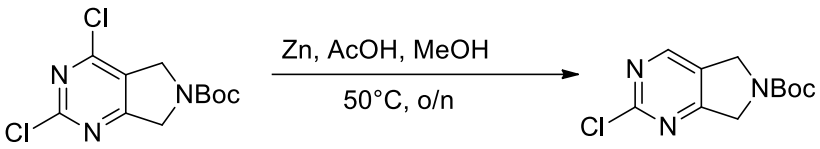
MX02044

1. Synthetic scheme:



2. Experimental section:

2.1 *tert*-Butyl 2-chloro-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (02044-1)

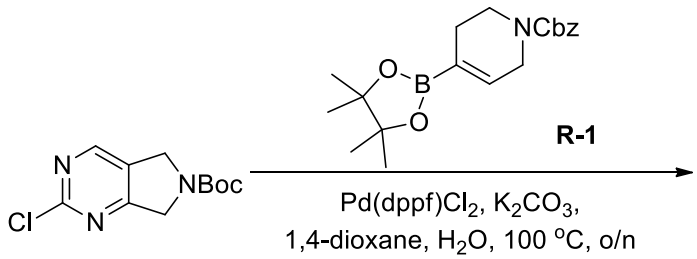


02044-0 **02044-1**

To a solution of *tert*-butyl 2,4-dichloro-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (300.0 mg, 1.03 mmol) in MeOH (10.0 mL) and AcOH (1.0 mL) was added Zn (338.0 mg, 5.17 mmol). Then the mixture was stirred at 50 °C overnight. The reaction mixture was concentrated and the crude product was extracted by DCM (20 mL*3) and water (20 mL). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica-CS 20 g, 40 mL/min, silica gel, UV 254) to afford the title product (202.0 mg, 84.8% yield) as yellow oil.

ESI-MS *m/z* calcd for $[C_{11}H_{14}ClN_3O_2]$ $[M+H]^+$: 256.1; found: 256.2

2.2*tert*-Butyl2-(1-((benzyloxy)carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (02044-2)



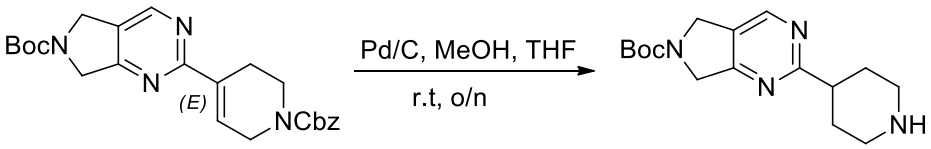
02044-1 **02044-2**

To a solution of *tert*-butyl 2-chloro-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (200.0 mg, 0.782 mmol) in

1,4-dioxane (5.0 mL) and H_2O (1.0 mL) were added benzyl4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (322.0 mg, 0.94 mmol), K_2CO_3 (324.0 mg, 2.35 mmol) and $Pd(dppf)Cl_2$ (32.0 mg, 0.04 mmol). The mixture was stirred at 100 °C overnight under N_2. The reaction mixture was concentrated and the crude product was extracted by DCM (20 mL*3) and water (20 mL). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica-CS 20 g, 40 mL/min, silica gel, UV 254) to afford the title product (255.0 mg, 74.6% yield) as an off-white solid.

ESI-MS *m/z* calcd for $[C_{24}H_{28}N_4O_4]$ $[M+H]^+$: 437.2; found: 437.2

2.3 *tert*-Butyl 2-(piperidin-4-yl)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (MX02044-3)

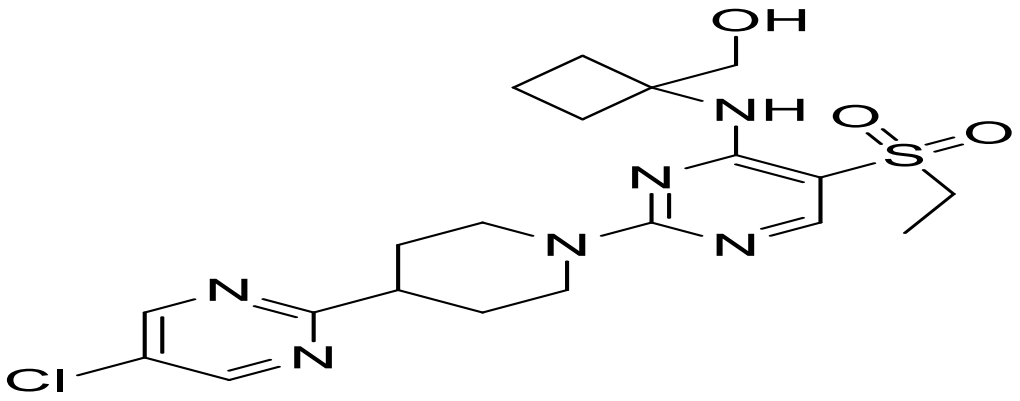


02044-2 **02044-3**

To a solution of *tert*-butyl2-(1-((benzyloxy)carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (255.0 mg, 0.584 mmol) in MeOH/THF (v/v=1:1,10.0 mL) was added Pd/C (50.0 mg, 0.256 mmol). The mixture was stirred under hydrogen atmosphere at room temperature overnight. The mixture was filtered and concentrated under reduced pressure to afford the title product (200.0 mg, 0.584 mmol, yield: 100%) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{16}H_{24}N_4O_2]$ $[M+H]^+$: 305.2; found: 305.2

2.4(*R*)-*tert*-Butyl2-(1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)piperidin-4-yl)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (02044-4)

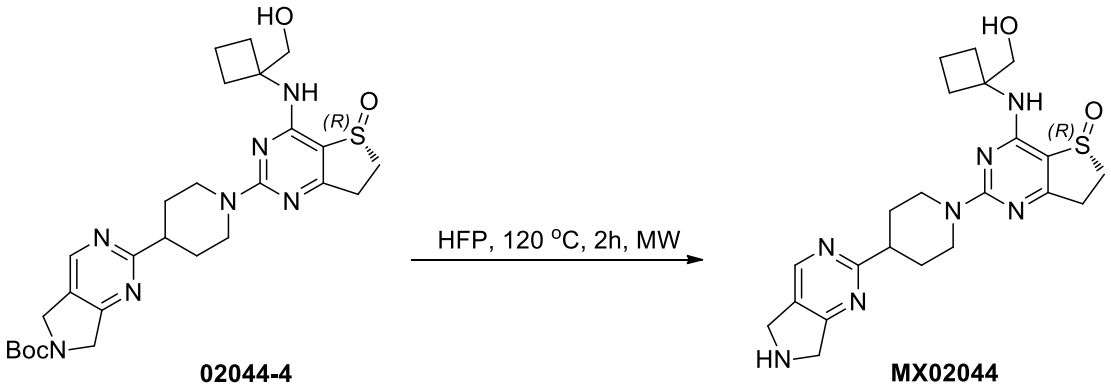


MX02138

To a solution of (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (90.0 mg, 0.313 mmol) in DMF (5.0 mL) and DIEA (1.0 mL) was added *tert*-butyl 2-(piperidin-4-yl)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (200.0 mg, 0.584 mmol). The mixture was stirred at 115 °C for 3 hours. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (MeOH/DCM = 0/1~1/10, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to afford the title product (165.0 mg, 95.0% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{27}H_{37}N_7O_4S]$ $[M+H]^+$: 556.3; found: 556.2

2.5(*R*)-2-(4-(6,7-Dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-yl)piperidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02044)



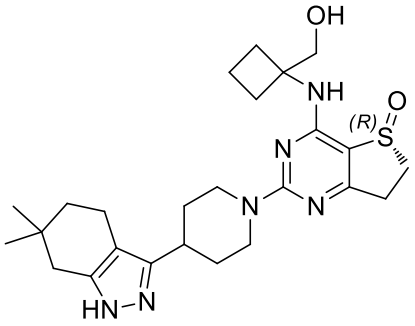
02044-4 **MX02044**

A solution of (*R*)-*tert*-butyl2-(1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)piperidin-4-yl)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (50.0 mg, 0.09 mmol) in HFP (2.0 mL) was stirred at 120 °C for 2 hours under microwave condition. The solvent was concentrated under reduced pressure and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10

μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (10.05 mg, 24.4% yield) as a white solid.

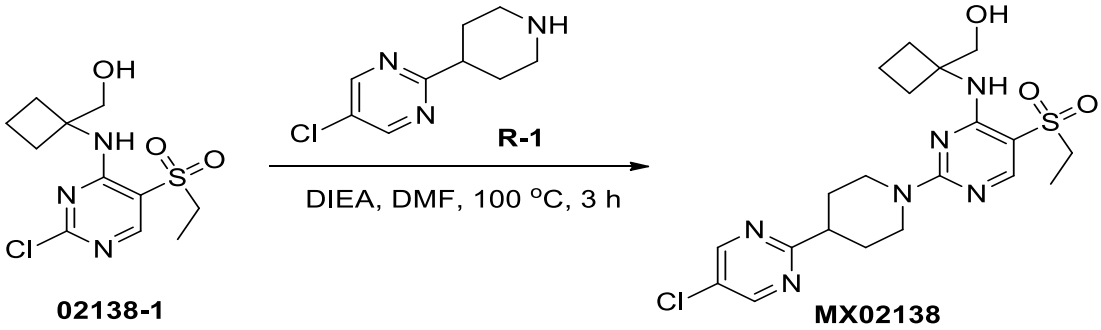
ESI-MS *m/z* calcd for $[C_{22}H_{29}N_7O_2S]$ $[M+H]^+$: 456.2; found: 456.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.39 (s, 1H), 4.86 (t, *J* = 5.6 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 2H), 4.58 – 4.51 (m, 1H), 4.08 (s, 2H), 3.98 (s, 2H), 3.70 – 3.68 (m, 2H), 3.45 – 3.37 (m, 1H), 3.24 – 3.12 (m, 2H), 3.07 – 2.98 (m, 2H), 2.96 – 2.28 (m, 2H), 2.38 – 2.25 (m, 2H), 2.18 – 2.13 (m, 2H), 1.94 – 1.91 (m, 2H),, 1.82 – 1.60 (m, 4H).



MX02053

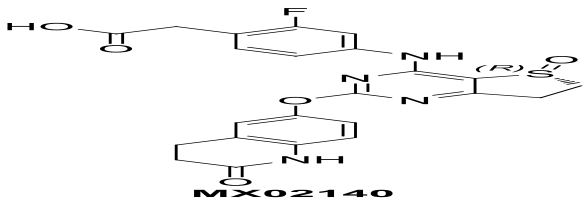
1. Synthetic scheme:



02138-1 **MX02138**

2. Experimental section:

2.1 4,4-Dimethyl-2-oxocyclohexanecarbaldehyde (02053-1)



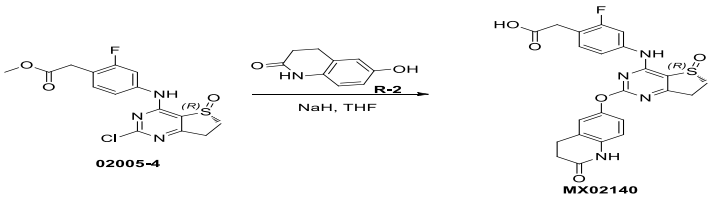
MX02140

To a suspension of NaH (60% dispersion in mineral oil, 349 mg, 8.72 mmol) in THF (10 mL) was added 3,3-dimethylcyclohexanone (1 g, 7.92 mmol) at 30°C. The reaction mixture was stirred for 1 hour. Then ethyl formate (1.2 g, 16.24 mol) was added to the solution at 35 °C and stirred for overnight at 40 °C. The mixture was acidified to pH 3 with 1 M HCl. The mixture

was extracted with EA (50 mL *2). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound (990 mg, 81.1% yield) as yellow oil.

ESI-MS *m/z* calcd for $[C_9H_{14}O_2]$ $[M+H]^+$: 155.1; found: 155.4

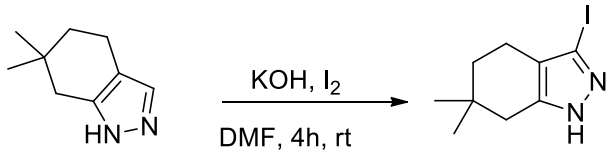
2.2 6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-indazole (02053-2)



To a solution of 4,4-dimethyl-2-oxocyclohexanecarbaldehyde (250 mg, 1.62 mmol) in MeOH (10 mL) was added a solution of hydrazine hydrate (82 mg, 1.64 mmol) in MeOH (5 mL) dropwise with heating under reflux over 15 minutes. The reaction mixture was concentrated under reduced pressure, EA (20 mL) and water (20 mL) were added, and the organic layer was separated. The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound (135 mg, 55.4% yield) as yellow oil.

ESI-MS *m/z* calcd for $[C_9H_{14}N_2]$ $[M+H]^+$: 151.1; found: 151.4

2.3 3-Iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole (02053-3)

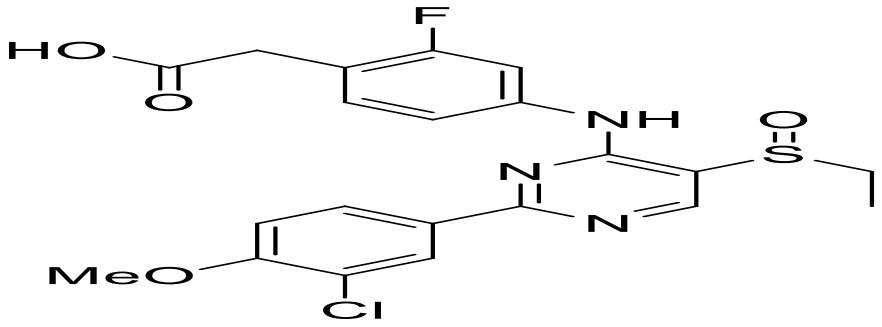


02053-2 **02053-3**

To a solution of 6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole (523 mg, 3.48 mmol) in DMF (10 mL) were added I_2 (3.68 g, 8.7 mmol) and KOH (967 mg, 17.23 mmol) at room temperature and the mixture was stirred for 4 hours. Then reaction was cooled in an ice bath and an aqueous solution of $NaHSO_3$ (2 g in 20 mL water) was added dropwise. More water (100 mL) was then added. A precipitate appeared and was filtered to afford the title compound (400 mg, 41% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_9H_{13}IN_2]$ $[M+H]^+$: 277.0; found: 277.1

2.4Benzyl-4-(6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (02053-4)



MX02147

To a solution of 3-iodo-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazole (229 mg, 0.83 mmol) and benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (285 mg, 0.83 mmol) in 1,4-dioxane/H_2O (12 mL, v/v 3:1) were added Pd(dppf)Cl_2 (18 mg, 0.02 mmol) and K_2CO_3 (344 mg, 2.49 mmol). After degassing the flask with three alternating vacuum and nitrogen purge cycles, the mixture was stirred for 3 hours at 60°C under nitrogen atmosphere. Then water (20 mL) was added and the mixture was extracted with EA (20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product which was purified by column chromatography (PE/EA = 0~1, Silica-CS 20 g, 30 mL/min, silica gel, UV 254) to afford the title compound (164 mg, 54.0 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{23}H_{28}N_2O_2]$ $[M+H]^+$: 365.2; found: 366.2

2.5 6,6-Dimethyl-3-(piperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-indazole (02053-5)

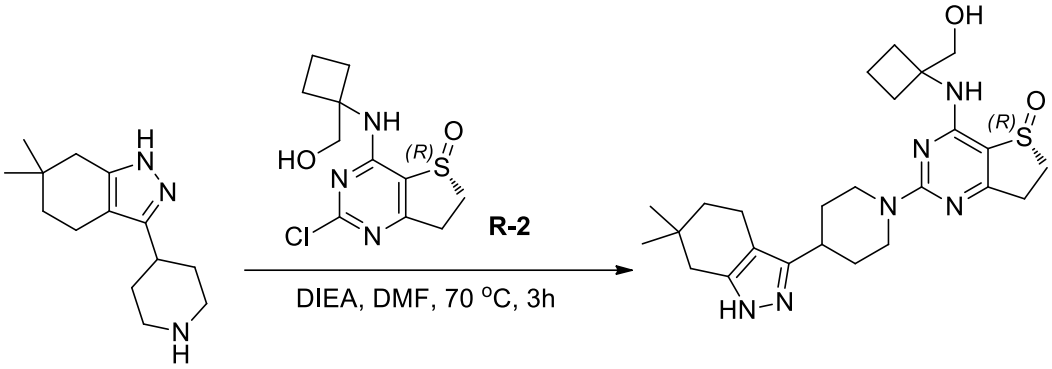


02053-4 **02053-5**

To a solution of benzyl-4-(6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (210 mg, 0.57 mmol) in MeOH (3 mL) was added Pd/C (20 mg). The reaction mixture was degassed and purged with H_2 for 3 times, then the mixture was stirred at room temperature overnight under H_2. Filtered to remove the Pd/C with diatomite. The filtrate was concentrated under reduced pressure to afford the title compound (120 mg, 89.5% yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{14}H_{23}N_3]$ $[M+H]^+$: 234.2; found: 234.4

2.6(*R*)-2-(4-(6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-indazol-3-yl)piperidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02053)

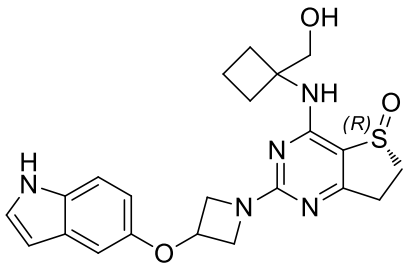


02053-5 MX02053

To a solution of (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (60.0 mg, 0.41 mmol) and DIEA (131 mg, 1.03 mmol) in DMF (7 mL) was added 6,6-dimethyl-3-(piperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-indazole (120 mg, 0.51 mmol). The mixture was then stirred for 3 hours at 70 °C. The reaction mixture was concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (20.75 mg, 8.33% yield) as a white solid.

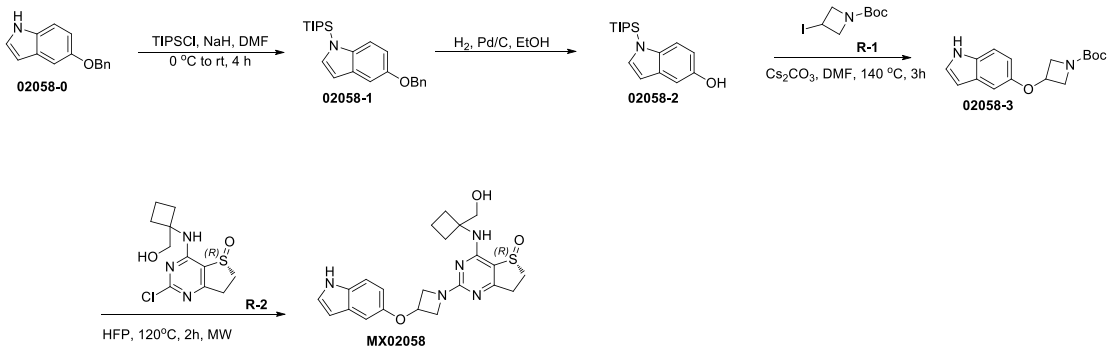
ESI-MS *m/z* calcd for $[C_{25}H_{36}N_6O_2S]$ $[M+H]^+$: 485.3; found: 485.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 – 11.82 (m, 1H), 7.38 – 7.30 (m, 1H), 4.84 (t, *J* = 5.6 Hz, 1H), 4.81 – 4.62 (m, 2H), 3.75 – 3.68 (m, 2H), 3.45 – 3.36 (m, 1H), 3.24 – 3.16 (m, 1H), 3.01 – 2.82 (m, 5H), 2.39 – 2.27 (m, 6H), 2.19 – 2.10 (m, 2H), 1.86 – 1.70 (m, 4H), 1.60 – 1.48 (m, 2H), 1.43 (t, *J* = 6.4 Hz, 2H), 0.93 (s, 6H).



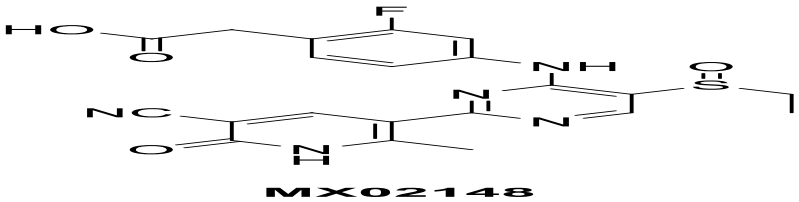
MX02058

1. Synthetic scheme:



2. Experimental section:

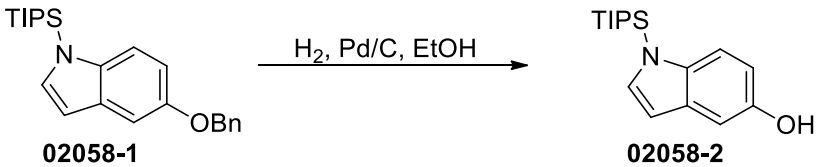
2.1 5-(Benzyloxy)-1-(triisopropylsilyl)-1*H*-indole (02058-1)



To a solution of 5-(benzyloxy)-1*H*-indole (3.0 g, 13.45 mmol) in anhydrous THF (20 mL) was added NaH (60%, 699 mg, 17.48 mmol) in THF (20 mL) dropwise at 0°C. The reaction mixture was allowed to slowly warm to room temperature over 30 minutes, Then chlorotriisopropylsilane (3.37 g, 17.48 mmol) was added dropwise over 5 minutes at 0°C. The resulting mixture was slowly warmed to room temperature and stirred for 4 hours. Then the reaction mixture was quenched at 0 °C with aq. NH_4Cl (20 mL) and extracted with Et_2O(15 mL*3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0~10%, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to obtain product (3.2 g, 62.69% yield) as a white solid.

ESI-MS *m/z* calcd for [$C_9H_{10}FNO_2$], NO MS was found

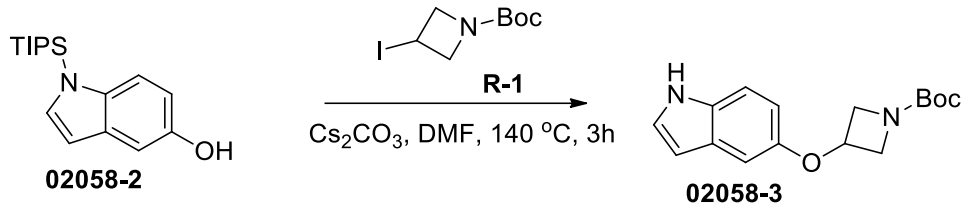
2.2 1-(Triisopropylsilyl)-1*H*-indol-5-ol (02058-2)



To a solution of 5-(benzyloxy)-1-(triisopropylsilyl)-1*H*-indole (3.2 g, 8.43 mmol) in EtOH (40.0 mL) was added wet Pd/C (120 mg) at room temperature. The reaction mixture was stirred overnight under hydrogen atmosphere. After filtered through a celite pad, the solvent was distilled off under reduced pressure to obtain product (2.3 g, 94.3% yield) as colorless oil.

ESI-MS *m/z* calcd for [$C_{17}H_{27}NOSi$] $[M+H]^+$: 290.2; found: 290.2

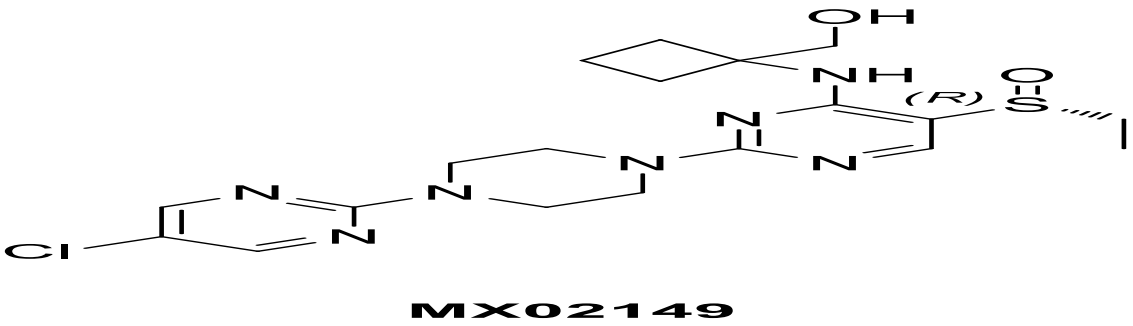
2.3 *tert*-Butyl-3-((1*H*-indol-5-yl)oxy)azetidine-1-carboxylate (02058-3)



To a solution of 1-(triisopropylsilyl)-1*H*-indol-5-ol (2.67 g, 9.22 mmol) and Cs_2CO_3 (9.0 g, 27.67 mmol) in DMF (50 mL) was added *tert*-butyl 3-iodoazetidine-1-carboxylate (3.1 g, 11.07 mmol). Then the mixture was stirred for 3 hours at 140 °C. The reaction mixture was concentrated and the crude product was extracted with EA (75 mL*2) and water (150 mL). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (EA/PE = 0~50%, Silica-CS 40 g, 50 mL/min, silica gel, UV 254) to afford the title product (480 mg, 81.5% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{16}H_{20}N_2O_3]$ $[M+H]^+$: 289.2; found: 289.1

2.4(*R*)-2-(3-((1*H*-Indol-5-yl)oxy)azetidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02058)



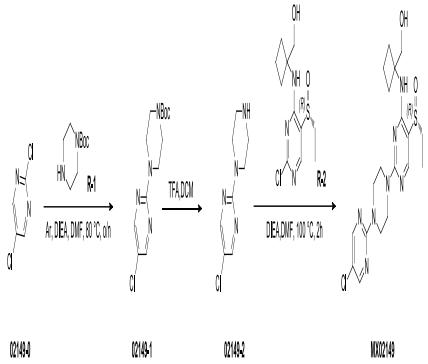
MX02149

A solution of *tert*-butyl 3-((1*H*-indol-5-yl)oxy)azetidine-1-carboxylate (50 mg, 0.17 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (49 mg, 0.17 mmol) in HFP (2.0 mL) was heated to 120 °C for 2 hours under microwave condition. The mixture was concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH4HCO3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title product (23.54 mg, 30.89% yield) as a white solid.

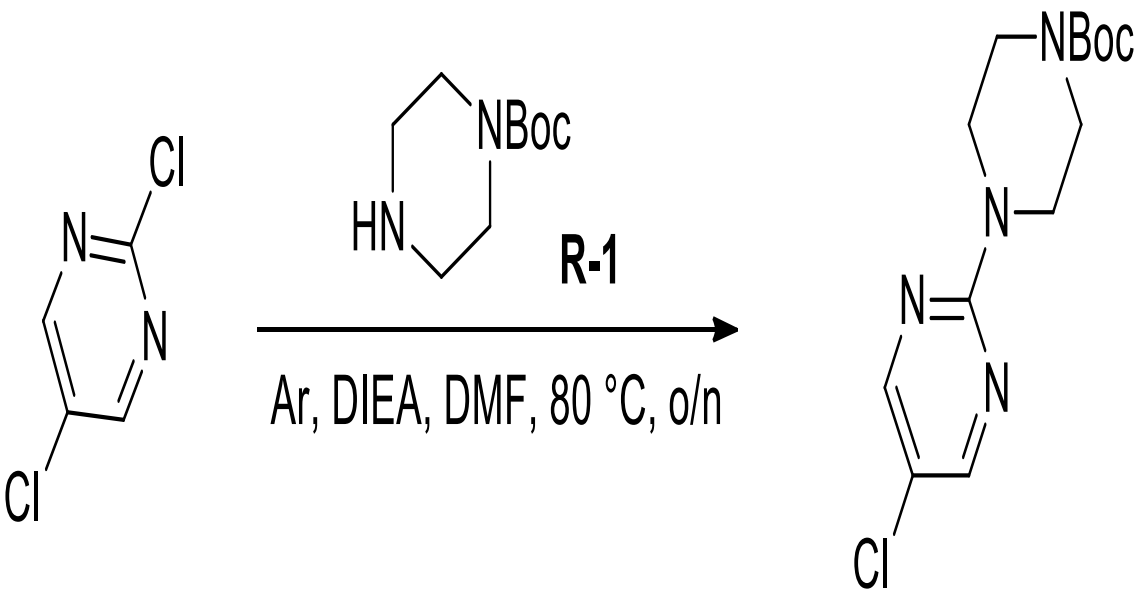
ESI-MS *m/z* calcd for $[C_{22}H_{25}N_5O_3S]$ $[M+H]^+$: 440.2; found: 440.0

^{1}H NMR (400 MHz,DMSO-d_6) δ 10.97 (s, 1H), 7.46 (s, 1H), 7.32 – 7.30 (m, 2H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.35 (t, *J* = 2.0 Hz, 1H), 5.11 – 5.06 (m, 1H),4.85 (t, *J* = 5.6 Hz, 1H), 4.45 (dd, *J* = 9.6, 6.4 Hz, 2H), 3.95 – 3.92 (m, 2H), 3.73 – 3.66 (m, 2H), 3.45 –3.37 (m, 1H), 3.25 –3.17 (m, 1H), 2.97 –2.84 (m, 2H), 2.38 –2.25 (m, 2H), 2.14 –2.10

(m, 2H), 1.82 –1.65 (m, 2H).



1. Synthetic scheme:



02149-0 **02149-1**

2. Experimental section:

2.1 *tert*-Butyl 4-(5-chloropyrimidin-2-yl)piperidine-1-carboxylate (A-3)



02149-1 **02149-2**

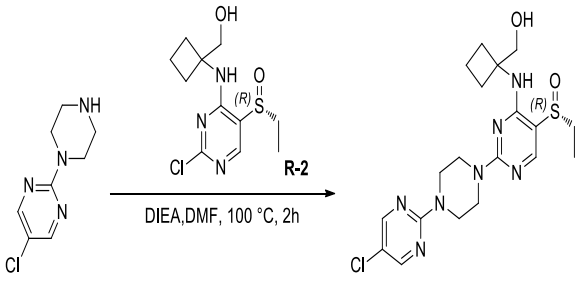
To a solution of

4- cyanopiperidine hydrochloride (3.1 g, 21.2 mmol) in 4N HCl/1,4-dioxane (10.6 mL, 42.4 mmol) was added MeOH (2.57 mL, 63.6mmol) while keeping the temperature below 10° C. The mixture was stirred for 6 hours at room temperature. The mixture was cooled to 5° C and 25 wt % NaOMe in methanol (13.74 g ,63.6 mmol) was added while maintaining the temperature below 15° C. The mixture was then stirred for 1 hour. 7N NH_3/MeOH (4.54 mL, 31.8 mmol) was added to the above mixture and stirred for 2 hours at room temperature. The mixture was concentrated under reduced pressure at 60°C to afford a 1,4-dioxane solution of crude compound that was without isolation.

The above 1,4-dioxane solution of intermediate compound was cooled to 0° C, and 25 wt % NaOMe in MeOH (11.45 g, 53.0 mmol) was added. The mixture was then stirred for 30 minutes. Compound (*Z*)-N-(2-chloro-3-(dimethylamino)allylidene)-*N*-methylmethanaminium Hexafluorophosphate (5.52 g, 18.02 mmol) was added to the above mixture in two portions at room temperature over 10 minutes and stirred for 6 hours at room temperature. The mixture was concentrated under reduced pressure. The crude product was dispersed in DCM (100 mL) and TEA (10.0 mL, 71.8 mmol), $(Boc)_2O$ (9.24 g, 42.4 mmol) were added, the mixture was stirred at room temperature for 3 hours. Water (100 mL) was added and separated, the water aqueous was extracted with DCM (150 mL*2). The combined organic phase was washed by saturated brine(150 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (EA/PE = 0/1~1/3, Silica-CS 80 g, 50 mL/min, silica gel, UV 254) to give the title product (2.50 g, 39.7% yield) as yellow oil.

ESI-MS *m/z* calcd for $[C_{14}H_{20}ClN_3O_2]$ $[M-56+H]^+$: 298.1; found: 242.3

2.2 5-Chloro-2-(piperidin-4-yl)pyrimidine (A-4)



02149-2 MX02149

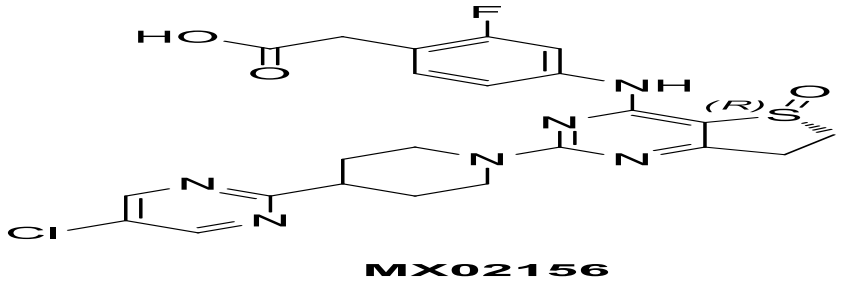
To a solution of

tert-butyl 4-(5-chloropyrimidin-2-yl)piperidine-1-carboxylate (100 mg, 0.335 mmol) in DCM (5.0 mL) was added TFA(0.5 mL). The reaction mixture was stirred at room temperature

overnight. The pH of the solution was adjusted to pH = 8 with TEA.The solvent was concentrated under reduced pressure. The crude product was used to next step directly (135 mg, 100% yield) as yellow oil.

ESI-MS *m/z* calcd for $[C_9H_{12}ClN_3]$ $[M+H]^+$: 198.1; found: 198.3

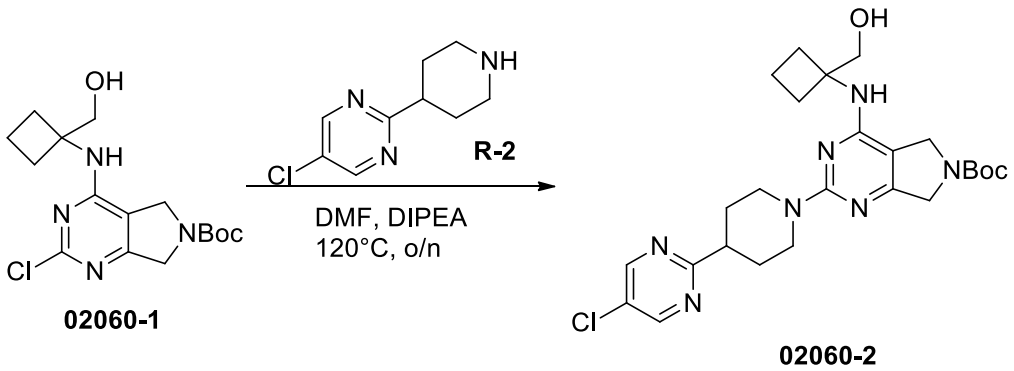
2.3*tert*-Butyl2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (02060-1)



To a solution of *tert*-butyl 2,4-dichloro-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (345.0 mg, 1.19 mmol) in MeCN (10.0 mL) and TEA (3.0 mL) was added (1-aminocyclobutyl)methanol (120.0 mg, 1.19 mmol). Then the mixture was stirred for 16 hours at 70 °C. The reaction mixture was concentrated and the crude product was extracted by DCM (20 mL*3) and water (20 mL). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/0, Silica-CS 20 g, 40 mL/min, silica gel, UV 254) to afford the title product (150.0 mg, 35.6% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{16}H_{23}ClN_4O_3]$ $[M+H]^+$: 355.1; found: 355.2

2.4*tert*-Butyl2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (02060-2)

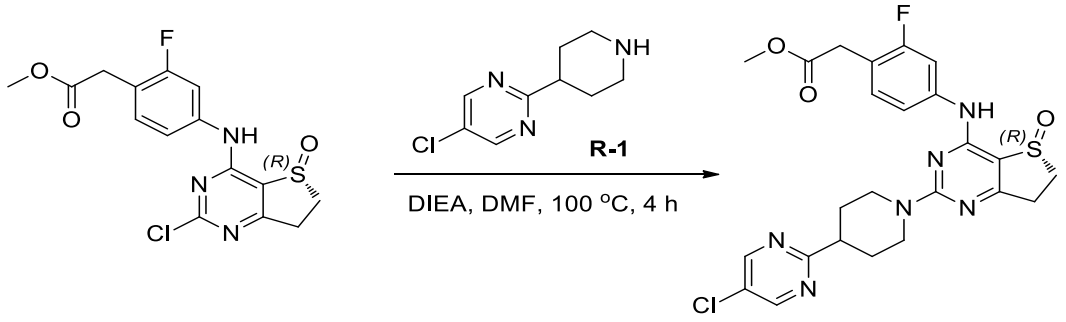


To a solution of *tert*-butyl2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-5*H*-pyrrolo[3,4-*d*]

pyrimidine-6(7*H*)-carboxylate (60.0 mg, 0.17 mmol) in DMF (4.0 mL) and DIEA (1.0 mL) was added 5-chloro-2-(piperidin-4-yl)pyrimidine (135 mg, 0.335 mmol). Then the mixture was stirred at 120 °C overnight. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (EA/PE = 0/1~1/0, Silica-CS 20 g, 40 mL/min, silica gel, UV 254) to afford the title product (40.0 mg, 45.6% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{25}H_{34}ClN_7O_3]$ $[M+H]^+$: 516.2; found: 516.0

2.5(1-((2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-yl)amino)cyclobutyl)methanol (MX02060)

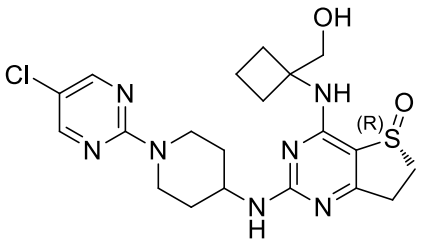


02156-0 **02156-1**

To a solution of *tert*-butyl 2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl) amino)-5*H*-pyrrolo[3,4-*d*]pyrimidine-6(7*H*)-carboxylate (40.0 mg, 0.078 mmol) in DCM (3.0 mL) was added TFA (0.3 mL). Then the mixture was stirred at room temperature overnight. The pH of the solution was adjusted to 7 with 1N aq. $NaHCO_3$. Solvent was removed under reduced pressure and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (19.05 mg, 59.0% yield) as a white solid.

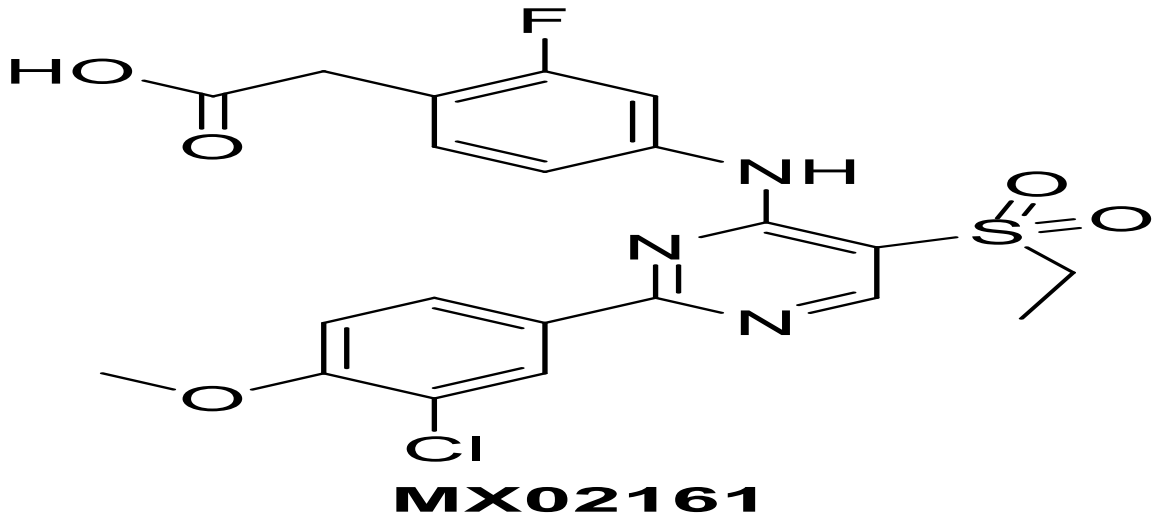
ESI-MS *m/z* calcd for $[C_{20}H_{26}ClN_7O]$ $[M+H]^+$: 416.2; found: 416.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 2H), 6.47 (s, 1H), 4.79 (t, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 12.8 Hz, 2H), 4.27 – 4.21 (m, 1H), 3.80 – 3.67 (m, 6H), 3.15 – 3.09 (m, 1H), 2.95 – 2.89 (m, 2H), 2.25 – 2.11 (m, 4H), 1.89 – 1.86 (m, 2H), 1.80 – 1.73 (m, 2H), 1.67 – 1.57 (m, 2H).



MX02063

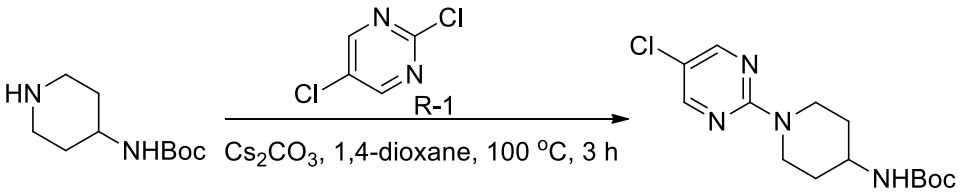
1. Synthetic scheme:



MX02161

2. Experimental section:

2.1 *tert*-Butyl (1-(5-chloropyrimidin-2-yl)piperidin-4-yl)carbamate (02063-1)

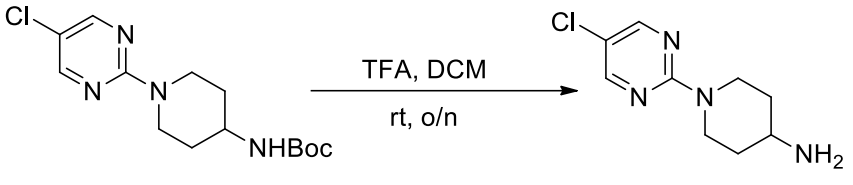


02063-0 02063-1

To a solution of *tert*-butyl piperidin-4-ylcarbamate (664.0 mg, 3.32 mmol) in 1,4-dioxane (8.0 mL) were added 2,5-dichloropyrimidine (450.0 mg, 3.02 mmol) and Cs_2CO_3 (1.97 g, 6.04 mmol) at room temperature. The reaction mixture was stirred for 3 hours at 100 °C. Water (30 mL) was added and the mixture was extracted with EA (30 mL*3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (EA/PE = 0~50%, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give the title product (800 mg, 84.6% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{14}H_{21}ClN_4O_2]$ $[M+H]^+$: 313.1; found: 313.2

2.2 1-(5-Chloropyrimidin-2-yl)piperidin-4-amine (02063-2)

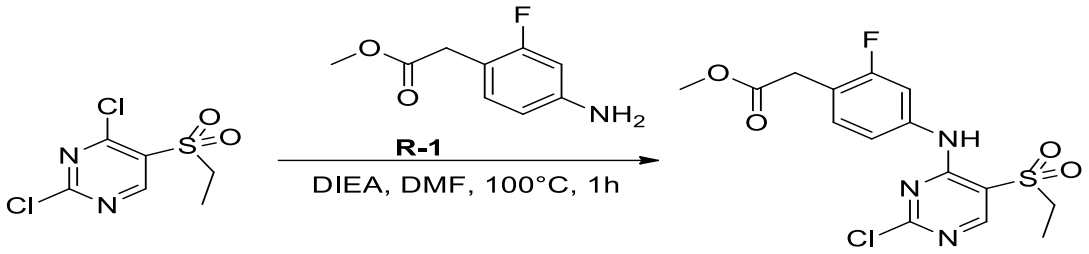


02063-1 **02063-2**

To a solution of *tert*-butyl (1-(5-chloropyrimidin-2-yl)piperidin-4-yl)carbamate (210 mg, 0.67 mmol) in DCM (5.0 mL) was added TFA (0.5mL). The reaction mixture was stirred at room temperature overnight. The solvent was concentrated under reduced pressure. The crude product was got the crude product used to next step directly (230 mg, 100% yield) as a yellow oil used to next step directly.

ESI-MS *m/z* calcd for $[C_9H_{13}ClN_4]$ $[M+H]^+$: 213.1; found: 213.2

2.3(*R*)-2-((1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)amino)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02063)

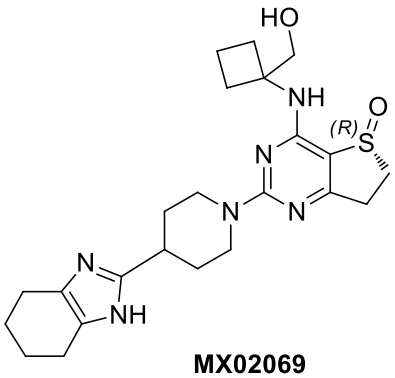


02161-1 **02161-2**

To a solution of 1-(5-chloropyrimidin-2-yl)piperidin-4-amine (230 mg, 0.67 mmol) in DMF (5.0 mL) and DIEA (1.0 mL) was added (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (100.0 mg, 0.347 mmol). The mixture was stirred for 16 hours at 80 °C. The reaction mixture was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (12 mg, 7.5% yield) as a white solid.

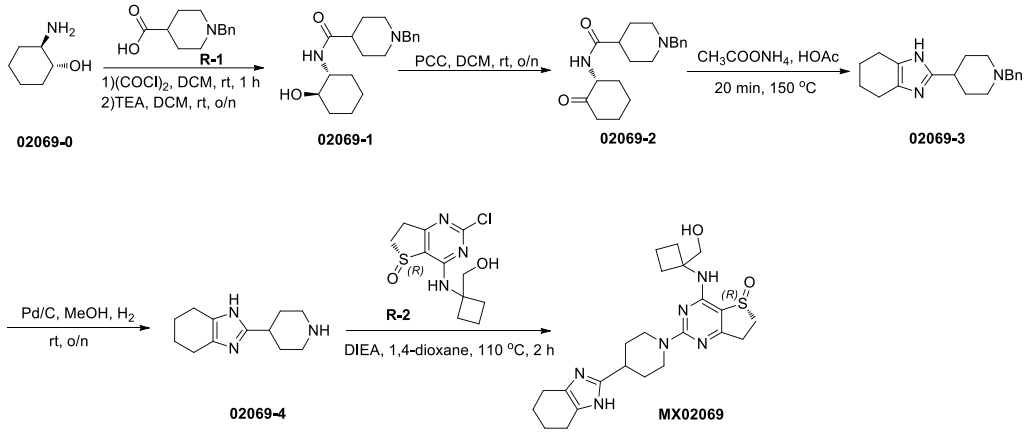
ESI-MS *m/z* calcd for $[C_{20}H_{26}ClN_7O_2S]$ $[M+H]^+$: 464.2; found: 464.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 2H), 7.31 – 7.24 (m, 2H), 4.87 (t, J = 5.6 Hz, 1H), 4.49 (d, J = 13.2 Hz, 2H), 3.94 – 3.90 (m, 1H), 3.72 (d, J = 5.2 Hz, 2H), 3.39 – 3.31 (m, 1H), 3.22 – 3.04 (m, 3H), 2.88 – 2.81 (m, 2H), 2.41 – 2.30 (m, 2H), 2.17 – 2.12 (m, 2H), 1.88 – 1.71 (m, 4H), 1.44 – 1.36 (m, 2H).



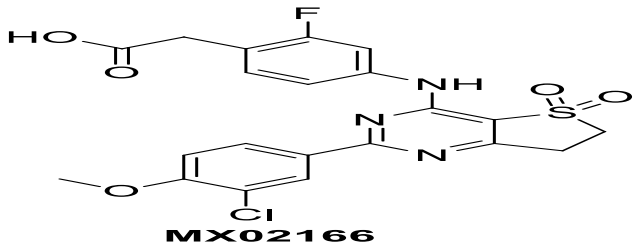
MX02069

1. Synthetic scheme:



2. Experimental section:

2.1 1-Benzyl-*N*-((1*R*,2*R*)-2-hydroxycyclohexyl)piperidine-4-carboxamide (02069-1)

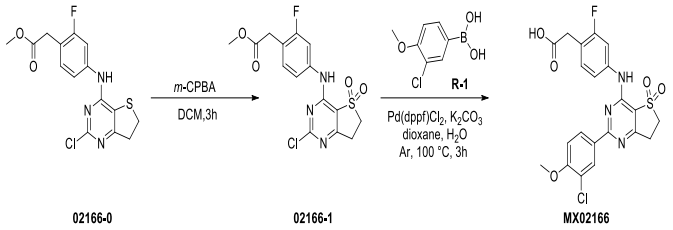


MX02166

To a solution of 1-benzylpiperidine-4-carboxylic acid (512 mg, 2.34 mmol) in DCM (8 mL) was added $(COCl)_2$ (358 mg, 2.82 mmol). The resulted reaction mixture was stirred at room temperature for 1 hour under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was added DCM (8 mL), (1*R*,2*R*)-2-aminocyclohexanol (270 mg, 2.34 mmol) and TEA (709 mg, 7.02 mmol), the mixture was stirred at room temperature overnight. LCMS showed the reaction was completely, the mixture was quenched with water (30 mL) and extracted with EA (50 mL *3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title product (602 mg, 81% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{19}H_{28}N_2O_2]$ $[M+H]^+$: 317.2; found: 317.3

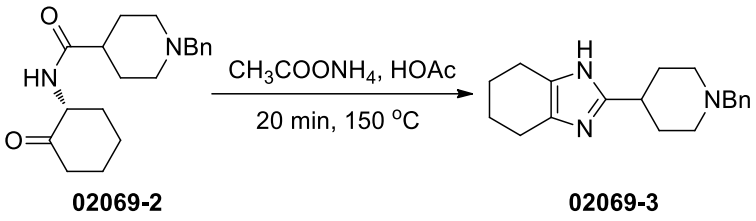
2.2 (*R*)-1-Benzyl-*N*-(2-oxocyclohexyl)piperidine-4-carboxamide (02069-2)



To a solution of 1-benzyl-*N*-((1*R*,2*R*)-2-hydroxycyclohexyl)piperidine-4-carboxamide (602 mg, 1.90 mmol) in DCM (15 mL) was added PCC (1.23 g, 5.71 mmol). The resulted reaction mixture was stirred at room temperature overnight under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated in vacuo. The crude product was quenched with water and extracted with EA (50 mL*3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title product (340 mg, 56% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{19}H_{26}N_2O_2]$ $[M+H]^+$: 315.2; found: 315.2

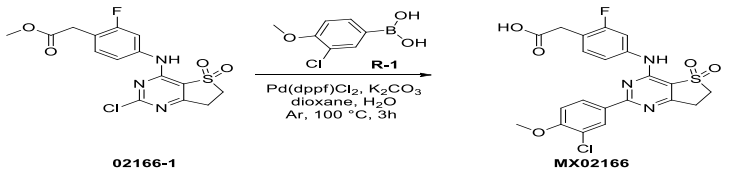
2.3 2-(1-Benzylpiperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazole (02069-3)



To a solution of (*R*)-1-benzyl-*N*-(2-oxocyclohexyl)piperidine-4-carboxamide (140 mg, 0.44 mmol) in HOAc (5 mL) was added CH_3COONH_4 (338 mg, 4.4 mmol). The resulted reaction mixture was stirred at 150 °C for 20 minutes under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated, the crude product was purified by reversed-phase chromatography ($MeCN/H_2O$ =1/20~1/1, C-18 column, 20 mL/min, UV 254) to afford the title product (72 mg, 55% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{19}H_{25}N_3]$ $[M+H]^+$: 296.2; found: 296.2

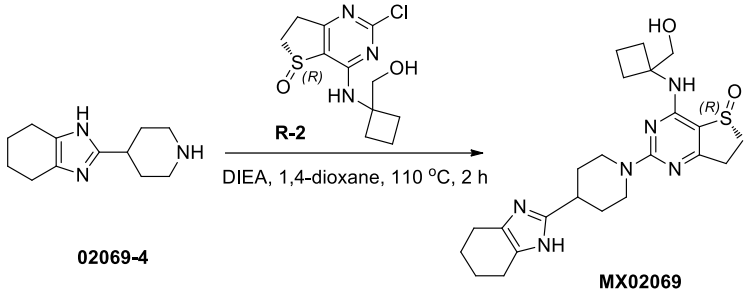
2.4 2-(Piperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazole (02069-4)



To a solution of 2-(1-benzylpiperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazole (72 mg, 0.24 mmol) in MeOH (3 mL) was added Pd/C (24 mg). The resulted reaction mixture was stirred at room temperature overnight under H_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was filtered and the filter was concentrated to afford the title product (40 mg, 80% yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{12}H_{19}N_3]$ $[M+H]^+$: 206.2; found: 206.4

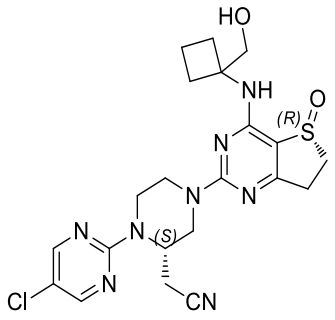
2.5(*R*)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(4-(4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazol-2-yl)piperidin-1-yl)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02069)



To a solution of 2-(piperidin-4-yl)-4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazole (40 mg, 0.20 mmol) in 1,4-dioxane (4 mL) was added (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (57 mg, 0.20 mmol) and DIEA (77 mg, 0.60 mmol). The resulted reaction mixture was stirred at 110 °C for 2 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (8.55 mg, 9% yield) as a white solid.

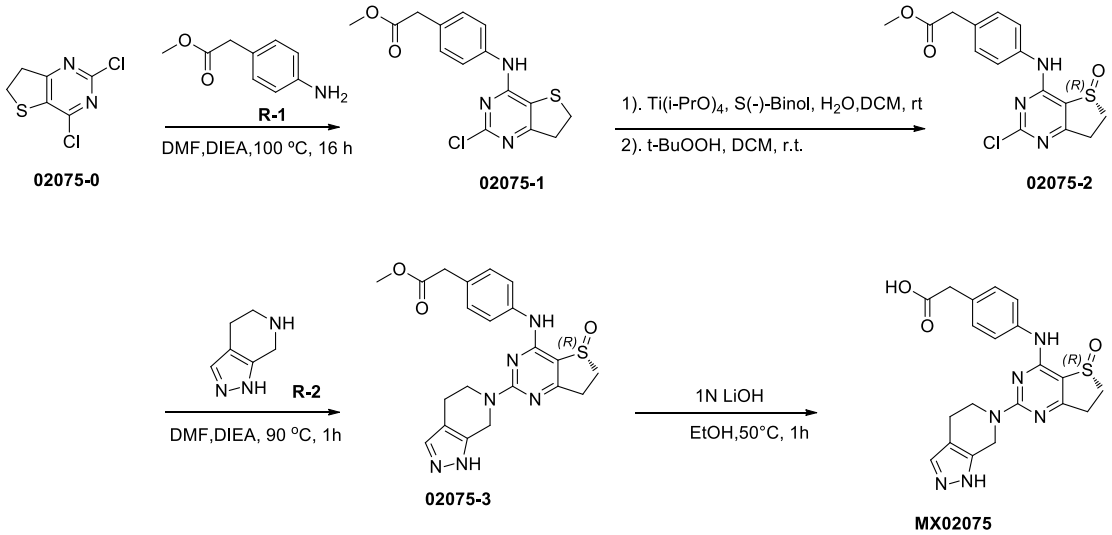
ESI-MS *m/z* calcd for $[C_{23}H_{32}N_6O_2S]$ $[M+H]^+$: 457.2; found: 457.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 7.37 (s, 1H), 4.86 (t, *J* = 5.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 2H), 3.72 – 3.69 (m, 2H), 3.45 – 3.36 (m, 1H), 3.23 – 3.16 (m, 1H), 3.03 – 2.83 (m, 5H), 2.41 – 2.26 (m, 6H), 2.19 – 2.13 (m, 2H), 1.85 – 1.73 (m, 4H), 1.68 – 1.66 (m, 4H), 1.58 – 1.54 (m, 2H) .



MX02010

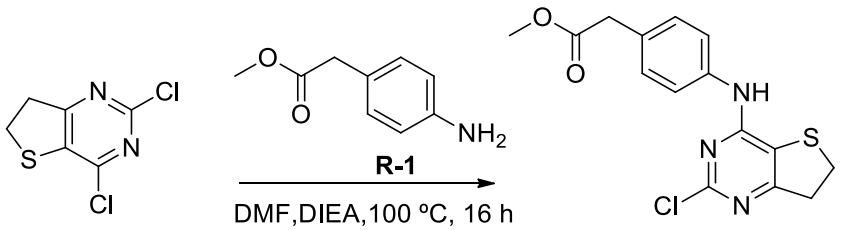
1. Synthetic scheme:



02075-0 | 02075-1 | 02075-2 | 02075-3 | MX02075

2. Experimental section:

2.1Methyl2-(4-((2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)phenyl)acetate (02075-1)



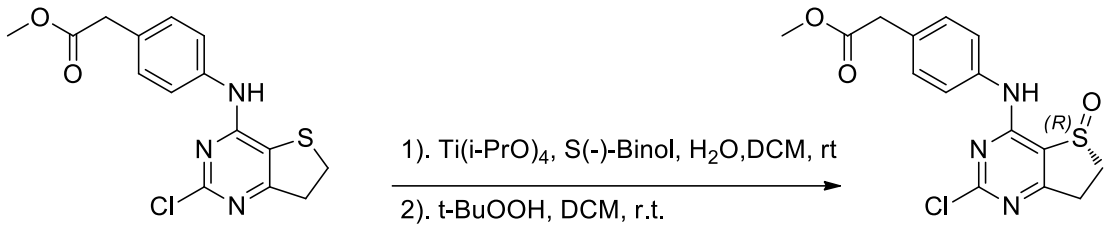
02075-0 | 02075-1

To a solution of 2,4-dichloro-6,7-dihydrothieno[3,2-*d*]pyrimidine (3 g, 14.48 mmol) and DIEA (5.61 g, 43.44 mmol) in DMF (50 mL) was added methyl 2-(4-aminophenyl)acetate (2.39 g, 14.48 mmol) at room temperature. The mixture was then stirred at 100 ºC overnight. Water (50 mL) was added and the mixture was extracted with DCM (70 mL*2). The combined organic layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (EA/PE = 0/1~1/2, Silica-CS 80 g, 50 mL/min, silica gel, UV 254) to afford

the title compound (3.11 g, 63.9% yield) as an orange solid.

ESI-MS *m/z* calcd for $[C_{15}H_{14}ClN_3O_2S]$ $[M+H]^+$: 336.1; found: 336.0

2.2(*R*)-Methyl-2-(4-((2-chloro-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetate (02075-2)

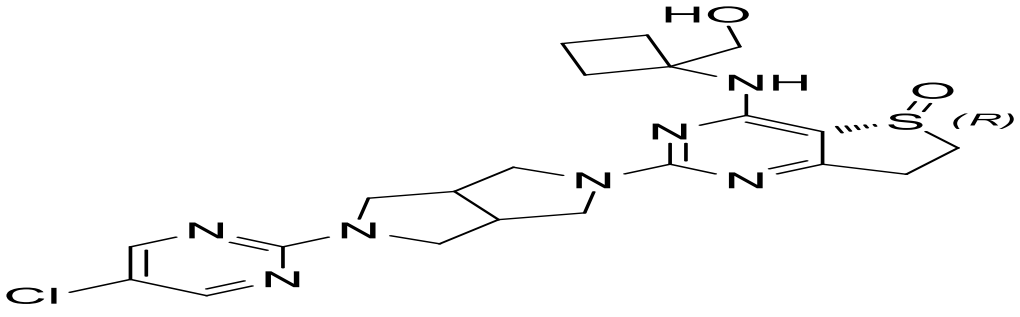


02075-1 **02075-2**

To a solution of methyl-2-(4-((2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (420 mg, 1.25 mmol) and S(-)-Binol (37.2 mg, 0.13 mmol) in DCM (10 mL) were added $Ti(i\text{-}PrO)_4$ (17.8 mg 0.06 mmol) and H_2O (22.5 mg, 1.25 mmol) . After degassing the flask with three alternating vacuum and nitrogen purge cycles, the mixture was stirred for 16 hours at room temperature. *t*-BuOOH (70% in water) (123.9 mg, 1.37 mmol) was added at once, then the mixture was stirred for 2 hours at room temperature.Water (20 mL) was added and the mixture was extracted with DCM (60 mL*3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (DCM/MeOH = 1/0~20/1, Silica-CS 40 g, 50 mL/min, silica gel, UV 254) to give the title product (367 mg, 83.4% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{15}H_{14}ClN_3O_3S]$ $[M+H]^+$:352.0; found: 352.0

2.3(*R*)-Methyl-2-(4-((2-(4,5-dihydro-1*H*-pyrazolo[3,4-c]pyridin-6(7*H*)-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)phenyl)acetate (02075-3)



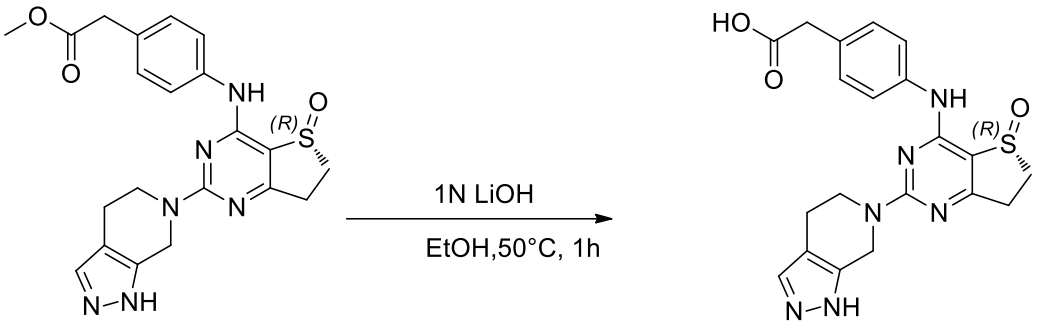
MX02016

To a solution of (*R*)-methyl 2-(4-((2-chloro-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetate (30.0 mg, 0.08 mmol) and DIEA (31.0 mg, 0.24 mmol) in DMF (5 mL) was added 4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine (9.8 mg, 0.08 mmol). The mixture was then stirred for 1 hour at 90 °C. The reaction mixture was purified by preparative

HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (27.0 mg, 72.2% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{21}H_{22}FN_6O_3S]$ $[M+H]^+$: 439.2; found: 439.0

2.4(*R*)-2-(4-((2-(4,5-Dihydro-1*H*-pyrazolo[3,4-c]pyridin-6(7*H*)-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)phenyl)acetic acid (MX02075)

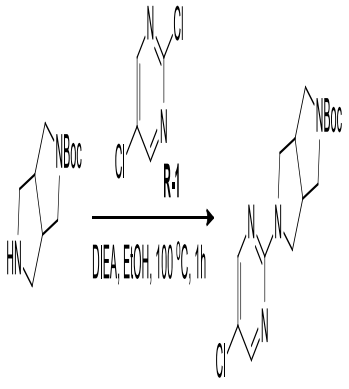


02075-3 MX02075

To a solution of (R)-Methyl 2-(4-((2-(4,5-dihydro-1*H*-pyrazolo[3,4-c]pyridin-6(7*H*)-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)phenyl)acetate (27.0 mg, 0.06 mmol) in EtOH (3 mL) was added 1N LiOH (0.6 mL, 0.6 mmol). The mixture was then stirred for 1 hour at 50 °C. The pH of the solution was adjusted to 6 with 1N aq. HCl. Solvent was removed under reduced pressure and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (11.57 mg, 35.1% yield) as a white solid.

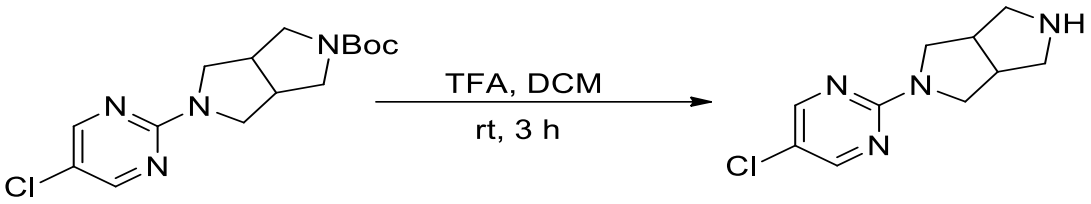
ESI-MS *m/z* calcd for $[C_{20}H_{20}N_6O_3S]$ $[M+H]^+$: 425.1; found: 425.0

^{1}H NMR (400 MHz, DMSO-d_6+D_2O) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.47 (s, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 4.89 – 4.87 (m, 2H), 4.02 – 4.00 (m, 2H) , 3.59 – 3.54 (m, 3H), 3.35 – 3.32 (m, 1H), 3.14 – 3.02 (m, 2H), 2.65 – 2.63 (m, 2H).



02016-0 02016-1

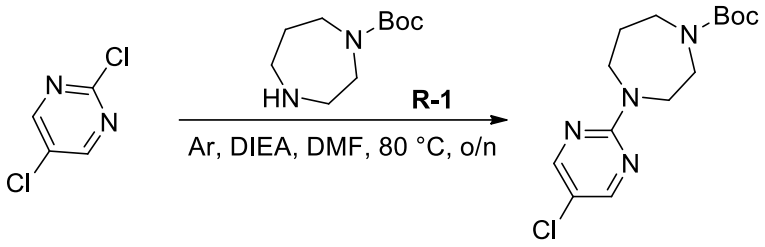
1. Synthetic scheme:



02016-1 **02016-2**

2. Experimental section:

2.1 *tert*-Butyl 4-(5-chloropyrimidin-2-yl)-1,4-diazepane-1-carboxylate (02077-1)

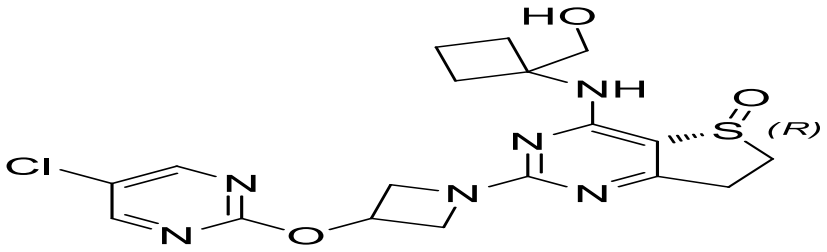


02077-0 **02077-1**

A mixture of 2,5-dichloropyrimidine (500 mg, 3.36 mmol), *tert*-butyl 1,4-diazepane-1-carboxylate (673 mg, 3.36 mmol) and DIEA (2.8 mL, 16.8 mmol) in DMF (20 mL) was stirred at 80 ºC overnight under argon. After cooling, the reaction mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0~1/9, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to give the title product (981 mg, 93.4 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{14}H_{21}ClN_4O_2]$ $[M+H]^+$: 313.1; found: 313.2

2.2 1-(5-Chloropyrimidin-2-yl)-1,4-diazepane (02077-2)

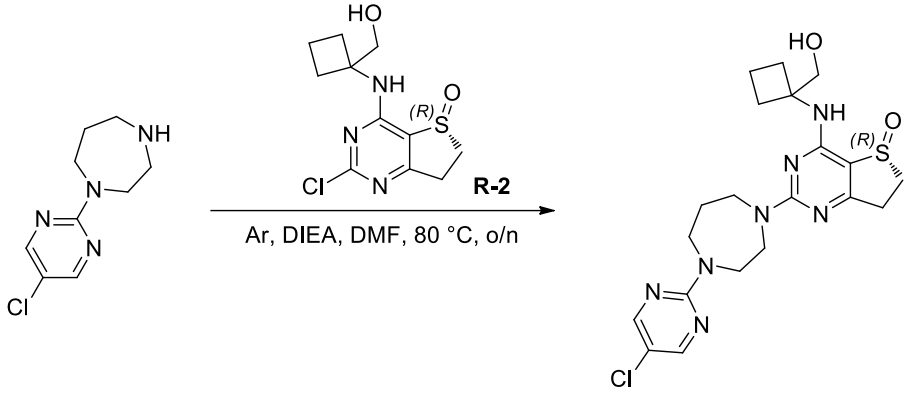


MX02019

To a mixture of *tert*-butyl 4-(5-chloropyrimidin-2-yl)-1,4-diazepane-1-carboxylate (200 mg, 0.64 mmol) in DCM (20 mL) was added TFA (4 mL) and stirred at 35 ºC for 2 hours under argon. After cooling, the mixture was concentrated to give the crude title product (136 mg, 99.9% yield) as pale yellow oil.

ESI-MS *m/z* calcd for $[C_9H_{13}ClN_4]$ $[M+H]^+$: 213.1; found: 213.2

2.3(*R*)-2-(4-(5-Chloropyrimidin-2-yl)-1,4-diazepan-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02077)

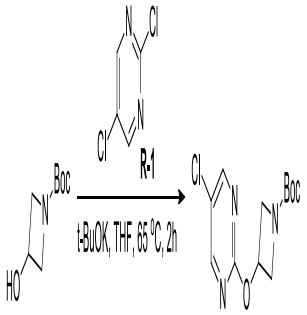


02077-2 MX02077

To a solution of 1-(5-chloropyrimidin-2-yl)-1,4-diazepane (68 mg, 0.32 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (92 mg, 0.32 mmol) in DMF (20 mL) was added DIEA (0.26 mL, 1.6 mmol) and stirred at 80 °C overnight under argon. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (MeOH/DCM = 0~1/9, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give crude product (90 mg) and then the crude prouduct was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (73.60 mg, 49.6 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{20}H_{26}ClN_7O_2S]$ $[M+H]^+$: 464.2; found: 463.9

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.38 (m, 2H), 7.30 (s, 1H), 4.85 (t, *J* =5.6 Hz, 1H), 3.95 – 3.78 (m, 4H), 3.74 – 3.57 (m, 6H), 3.42 – 3.36 (m, 1H), 3.23 – 3.15 (m, 1H), 2.94 – 2.81 (m, 2H), 2.36 – 2.28 (m, 2H), 2.16 – 2.14 (m, 2H), 1.86 – 1.72 (m, 4H).



02019-0 02019-1

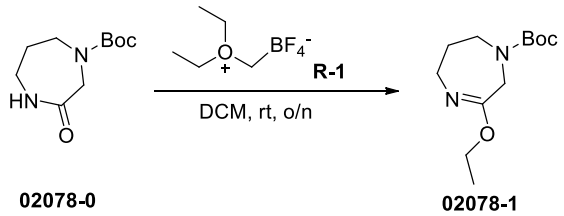
1. Synthetic scheme:



02019-1 02019-2

2. Experimental section:

2.1 *tert*-Butyl 3-ethoxy-2,5,6,7-tetrahydro-1*H*-1,4-diazepine-1-carboxylate (02078-1)

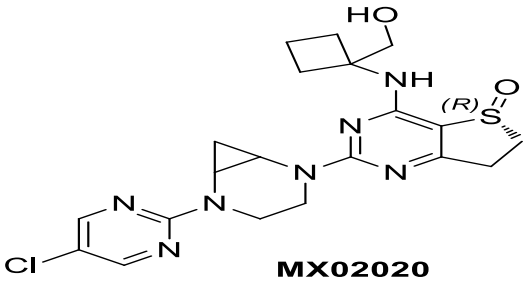


02078-0 02078-1

To a solution of *tert*-butyl 3-oxo-1,4-diazepane-1-carboxylate (500 mg, 2.34 mmol) in DCM (10 mL) was added Triethyloxonium tetrafluoroborate (613 mg, 3.50 mmol). The resulted reaction mixture was stirred at room temperature overnight under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the mixture was quenched with aq.$NaHCO_3$ (50 mL) and extracted with EA (50 mL*3). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title product (525 mg, 93% yield) as yellow oil.

ESI-MS *m/z* calcd for $[C_{12}H_{22}N_2O_3]$ $[M+H]^+$: 243.2; found: 243.3

2.2 *tert*-Butyl 3-(2-(methoxycarbonyl)hydrazinyl)-2,5,6,7-tetrahydro-1*H*-1,4-diazepine-1-carboxylate (02078-2)



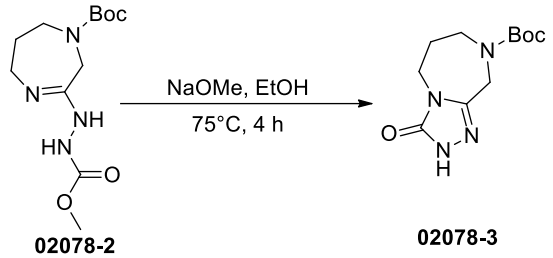
MX02020

To a solution of *tert*-butyl 3-ethoxy-2,5,6,7-tetrahydro-1*H*-1,4-diazepine-1-carboxylate

(525 mg, 2.17 mmol) in MeOH (5 mL) was added methyl hydrazinecarboxylate (195 mg, 2.17 mmol). The resulted reaction mixture was stirred at room temperature for 16 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by reversed-phase chromatography (MeCN/H_2O =1/20~1/1, C-18 column, 30 mL/min, UV 254) to afford the title product (126 mg, 20% yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{12}H_{22}N_4O_4]$ $[M+H]^+$: 287.2; found: 287.1

2.3*tert*-Butyl3-oxo-5,6,7,9-tetrahydro-2*H*-[1,2,4]triazolo[4,3-*a*][1,4]diazepine-8(3*H*)-carboxylate (02078-3)

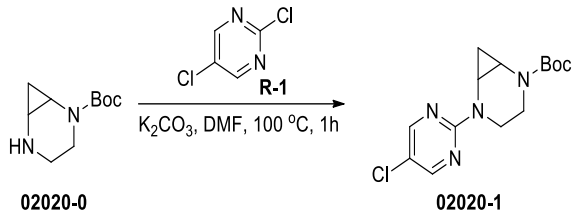


02078-2 02078-3

To a solution of *tert*-Butyl 3-(2-(methoxycarbonyl)hydrazinyl)-2,5,6,7-tetrahydro-1*H*-1,4-diazepine-1-carboxylate (126 mg, 0.44 mmol) in EtOH (3 mL) was added NaOMe (24 mg, 0.44 mmol). The resulted reaction mixture was stirred at 75 °C for 4 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by reversed-phase chromatography (MeCN/H_2O =1/20~1/1, C-18 column, 20 mL/min, UV 254) to afford the title product (61 mg, 55% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{11}H_{18}N_4O_3]$ $[M+H]^+$: 255.1; found: 255.

2.4 6,7,8,9-Tetrahydro-2*H*-[1,2,4]triazolo[4,3-*a*][1,4]diazepin-3(5*H*)-one (02078-4)

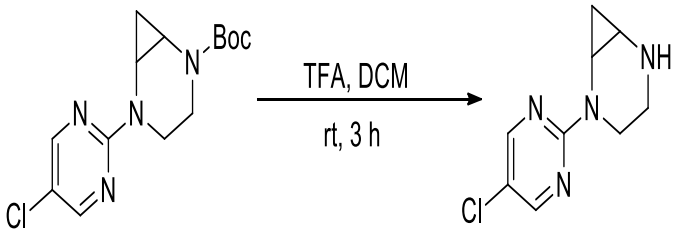


02020-0 02020-1

To a solution of *tert*-butyl 3-oxo-5,6,7,9-tetrahydro-2*H*-[1,2,4]triazolo[4,3-*a*][1,4]diazepine-8(3*H*)-carboxylate (61 mg, 0.24 mmol) in DCM (2 mL) was added TFA (0.2 mL). The resulted reaction mixture was stirred at room temperature for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the mixture was concentrated to afford the title product (33 mg, 89% yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{12}H_{22}N_4O_4]$ $[M+H]^+$: 155.1; found: 155.3

2.5(*R*)-8-(4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)-6,7,8,9-tetrahydro-2*H*-[1,2,4]triazolo[4,3-*a*][1,4]diazepin-3(5*H*)-one (MX02078)

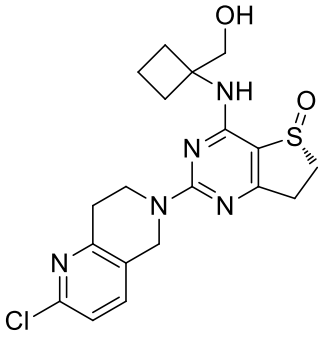


02020-1 02020-2

To a solution of 6,7,8,9-tetrahydro-2*H*-[1,2,4]triazolo[4,3-*a*][1,4]diazepin-3(5*H*)-one (33 mg, 0.21 mmol) in DMF (3 mL) were added (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (60 mg, 0.21 mmol) and DIEA (81 mg, 0.63 mmol). The resulted reaction mixture was stirred at 100 °C for 2 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (7.13 mg, 8% yield) as a white solid.

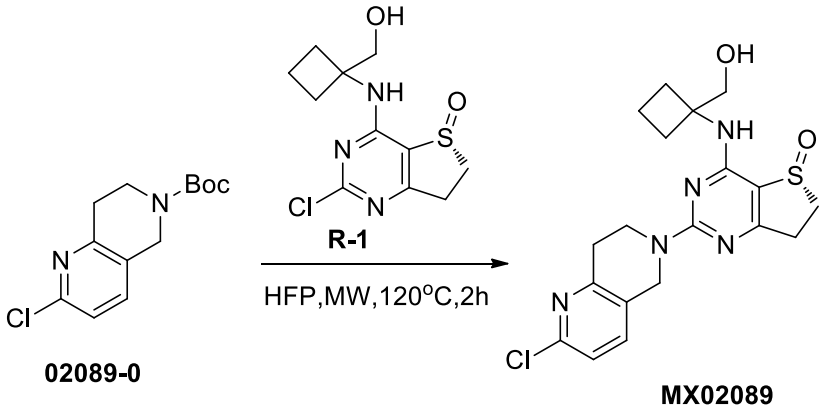
ESI-MS *m/z* calcd for $[C_{17}H_{23}N_7O_3S]$ $[M+H]^+$: 406.2; found: 406.2

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 7.52 – 7.38 (m, 1H), 4.83 – 4.72 (m, 3H), 4.04 – 3.94 (m, 2H), 3.80 – 3.70 (m, 4H), 3.44 – 3.36 (m, 1H), 3.23 – 3.16 (m, 1H), 2.95 – 2.83 (m, 2H), 2.37 – 2.14 (m, 4H), 1.77 – 1.71 (m, 4H).



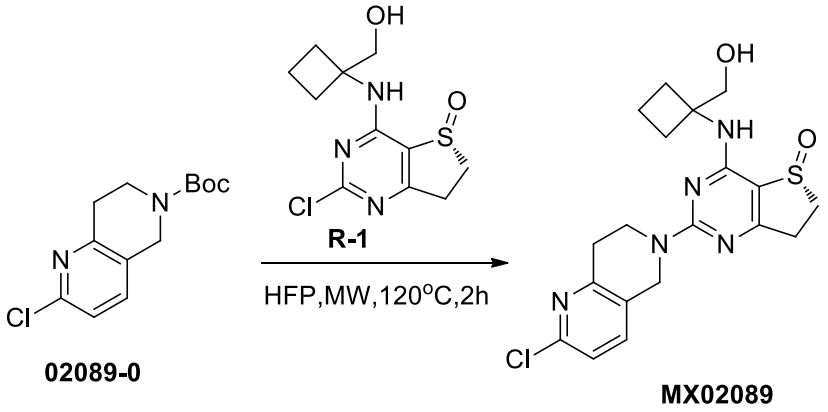
MX02089

1. Synthetic scheme:



2. Experimental section:

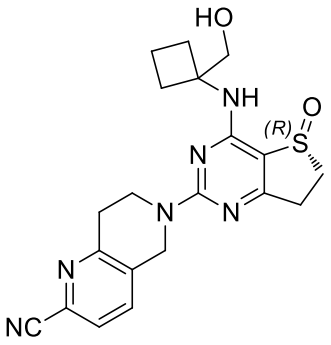
2.1(*R*)-2-(2-Chloro-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02089)



A solution of *tert*-butyl 2-chloro-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (40 mg, 0.148 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (40 mg, 0.138 mmol) in HFP (3.0 mL) was stirred at 120 °C for 2 hours under microwave condition. Water (10 mL) was added and the mixture was extracted with DCM (10 mL*2). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title compound (16.6 mg, 19.1% yield) as a white solid.

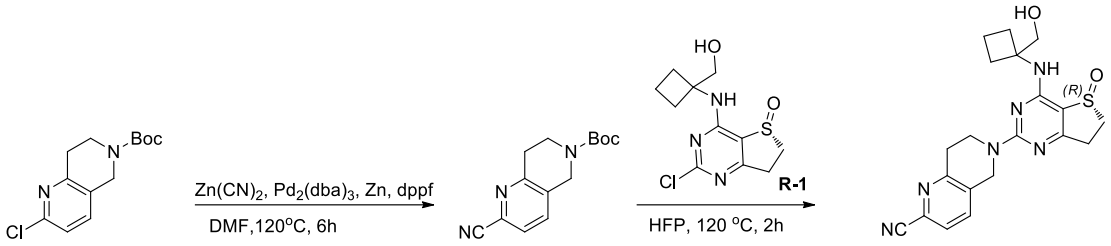
ESI-MS *m/z* calcd for [$C_{19}H_{22}ClN_5O_2S$] $[M+H]^+$: 420.12; found: 420.0

^{1}H NMR (400 MHz, DMSO-d_6) δ7.76 (d, *J* = 8.4 Hz, 1H),7.52 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 4.90 – 4.86 (m, 3H), 4.06 – 4.04 (m, 2H), 3.75 – 3.74 (m, 2H), 3.43 – 3.39 (m, 1H), 3.22 – 3.19 (m, 1H), 2.99 – 2.94 (m, 1H), 2.90 – 2.86 (m, 3H), 2.42 – 2.29 (m, 2H), 2.21 – 2.19 (m, 2H), 1.80 – 1.78 (m, 2H).



MX02090

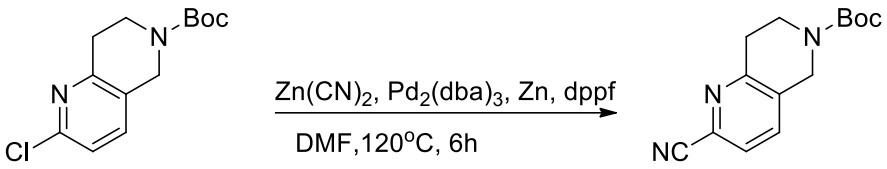
1. Synthetic scheme:



02090-0 **02090-1** **MX02090**

2. Experimental section:

2.1 *tert*-Butyl 2-cyano-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (02090-1)

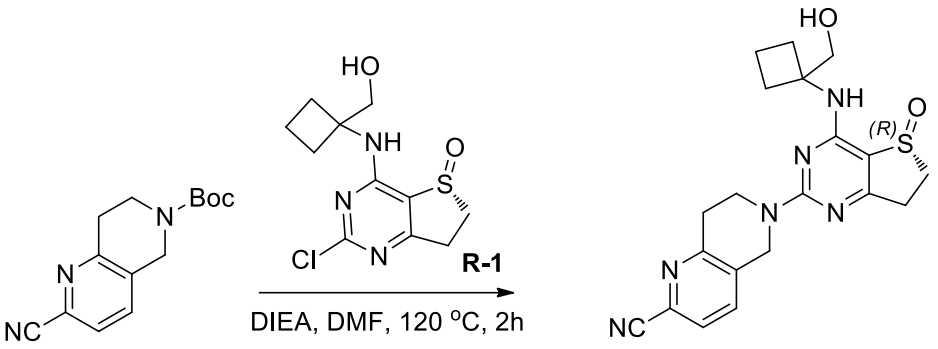


02090-0 **02090-1**

To a solution of *tert*-butyl 2-chloro-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (230 mg, 0.86 mmol) in DMF (15 mL) were added Zn (562.4 mg, 8.6 mmol), $Zn(CN)_2$ (1.01 g, 8.6 mmol), $Pd_2(dba)_3$ (238.1 mg, 0.26 mmol) and dppf (144.1 mg, 0.26 mmol). The reaction mixture was heated to 120°C for 6 hours, cooled to room temperature and concentrated. Water (10 mL) was added and the mixture was extracted with DCM (10 mL*2). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (EA/PE = 0~1/2, Silica-CS 12 g, 30 mL/min, silica gel, UV 254) to afford the title compound (167 mg, 75.2% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{14}H_{17}N_3O_2]$ $[M+H]^+$: 260.1; found: 260.2

2.2(*R*)-6-(4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carbonitrile (MX02090)

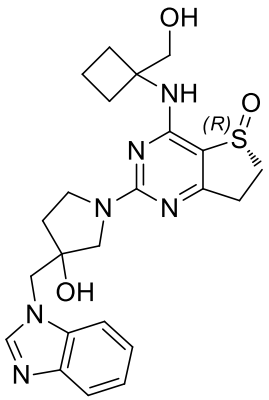


02090-1 **MX02090**

A solution of *tert*-butyl 2-cyano-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (147 mg, 0.57 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (164 mg, 0.57mmol) in HFP (3.0 mL) was stirred at 120 °C for 2 hours under microwave condition. Water (10 mL) was added and the mixture was extracted with DCM (10 mL*2). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title compound (16.0 mg, 6.9% yield) as a white solid.

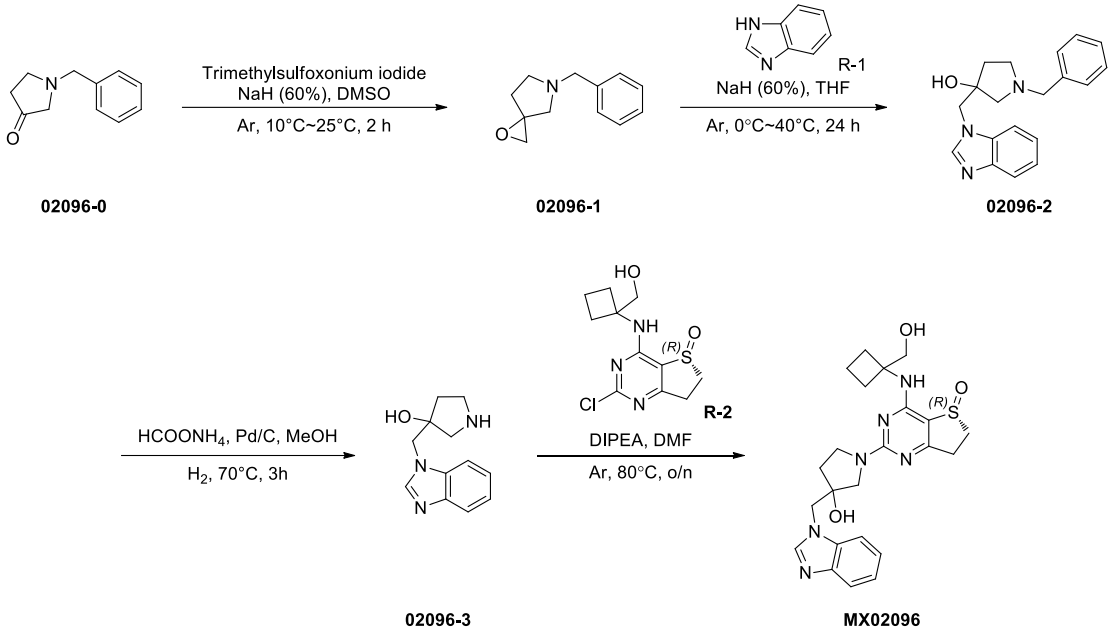
ESI-MS *m/z* calcd for $[C_{20}H_{22}N_6O_2S]$ $[M+H]^+$: 411.2; found: 411.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.55 (s, 1H), 5.01 (s, 2H), 4.86 (t, *J* = 5.6 Hz, 1H), 4.09 (t, *J* = 5.2 Hz, 2H), 3.78 – 3.73 (m, 2H), 3.47 – 3.39 (m, 1H), 3.25 – 3.17 (m, 1H), 2.99 – 2.85 (m, 4H), 2.39 – 2.20 (m, 4H), 1.86 – 1.71 (m, 2H).



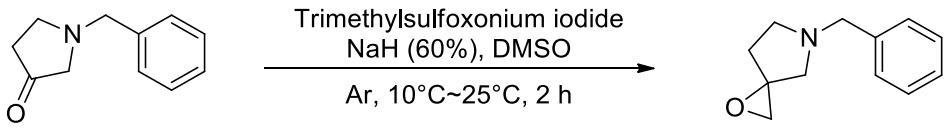
MX02096

1. Synthetic scheme:



2. Experimental section:

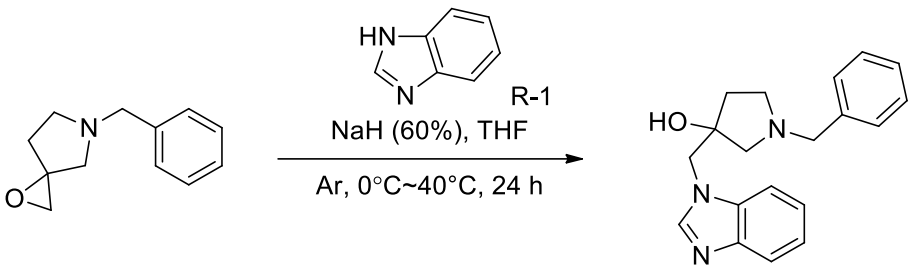
2.1 5-Benzyl-1-oxa-5-azaspiro[2.4]heptane (02096-1)



To a suspension of NaH (60%, 300 mg, 7.41 mmol) in DMSO (10 mL) was added trimethylsulfoxonium iodide (1.38 g, 6.27 mmol) in portion at 10 ºC and the reaction was stirred at 25 ºC for 1 hour under argon. A solution of 1-benzylpyrrolidin-3-one (1.0 g, 5.7 mmol) in DMSO (11 mL) was added and the reaction was stirred at 25 ºC for 2 hours. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and extracted with EA (50 mL*4) The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (EA/PE = 0~1/1, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to give the crude title product (326 mg, 30.2 % yield) as pale yellow oil.

ESI-MS *m/z* calcd for $[C_{12}H_{15}NO]$ $[M+H]^+$: 190.1; found: 190.1

2.2 3-((1*H*-Benzo[*d*]imidazol-1-yl)methyl)-1-benzylpyrrolidin-3-ol (02096-2)



02096-1 **02096-2**

To a suspension of NaH (60%, 96 mg, 2.4 mmol) in THF (6 mL) was added 1*H*-benzo[*d*]imidazole (142 mg, 1.2 mmol) in portion at 0 ºC and the reaction was stirred at 0 ºC for 1 hour under argon. A solution of 5-benzyl-1-oxa-5-azaspiro[2.4]heptane (226 mg, 1.2 mmol) in THF (4 mL) was added and the reaction was stirred at 40 ºC for 24 hours. The reaction mixture was quenched with water (20 mL) and extracted with EA (50 mL*3). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (MeOH/DCM = 0~1/9, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to give the crude title product (245 mg, 66.7 % yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{19}H_{21}N_3O]$ $[M+H]^+$: 308.2; found: 308.2

2.3 3-((1*H*-Benzo[*d*]imidazol-1-yl)methyl)pyrrolidin-3-ol (02096-3)

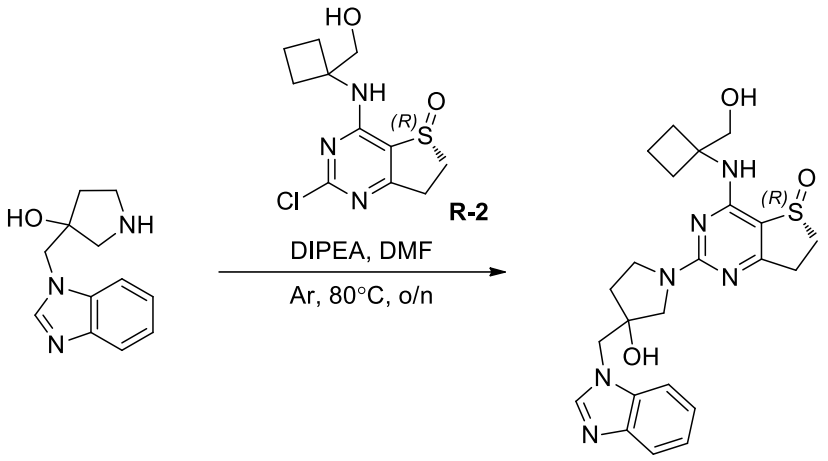


MX02025

To a solution of 3-((1*H*-benzo[*d*]imidazol-1-yl)methyl)-1-benzylpyrrolidin-3-ol (100 mg, 0.33 mmol) and $HCOONH_4$ (250 mg, 3.96 mmol) in MeOH (20 mL) was added Pd/C (30 mg, 30 % weight) and then the mixture was stirred at 70 ºC for 3 hours under hydrogen. After cooling, the reaction mixture was filtered under reduce pressure. The filtrate was evaporated under reduce pressure to remove solvent. The crude product was purified by reversed-phase chromatography ($MeCN/H_2O$ =0 ~ 3/17, C-18 column, 50 mL/min, UV 214) to give the title product (40 mg, 56.6 % yield) as a pale yellow solid.

ESI-MS *m/z* calcd for $[C_{12}H_{15}N_3O]$ $[M+H]^+$: 218.1; found: 218.1

2.4(5*R*)-2-(3-((1*H*-Benzo[*d*]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02096)

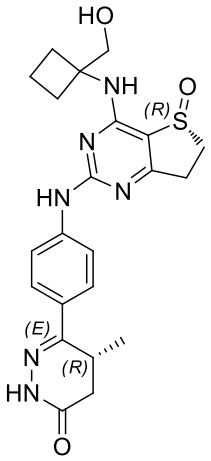


02096-3 **MX02096**

To a solution of 3-((1*H*-benzo[*d*]imidazol-1-yl)methyl)pyrrolidin-3-ol (10 mg, 0.05 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (14 mg, 0.05 mmol) in DMF (5 mL) was added DIEA (0.04 mL, 0.25 mmol) and then the mixture was at 80 °C overnight under argon. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (MeOH/DCM = 0~1/4, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give crude product (20 mg) and then the crude prouduct was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (7.72 mg, 27.3 % yield) as a white solid.

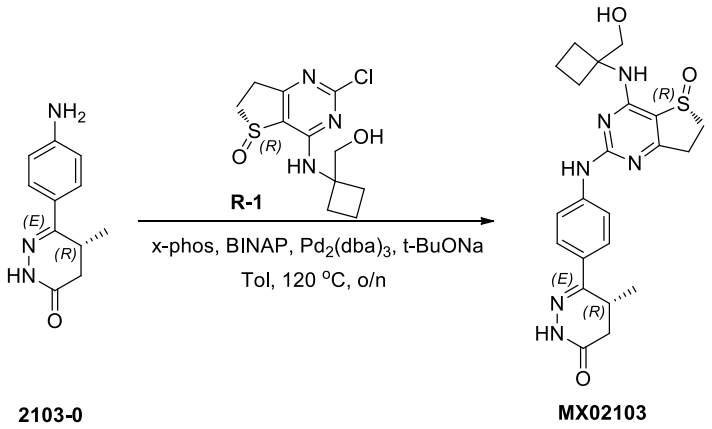
ESI-MS *m/z* calcd for [$C_{23}H_{28}N_6O_3S$] $[M+H]^+$: 469.2; found: 469.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 – 8.14 (m, 1H) 7.70 – 7.63 (m, 2H), 7.27 – 7.17 (m, 3H), 5.33 – 5.29 (m, 1H), 4.87 – 4.76 (m, 1H), 4.52 – 4.41 (m, 2H), 3.73 – 3.49 (m, 5H), 3.44 – 3.35 (m, 2H), 3.22 – 3.15 (m, 1H), 2.94 – 2.80 (m, 2H), 2.39 – 2.22 (m, 2H), 2.16 – 1.92 (m, 3H), 1.83 – 1.60 (m, 3H).



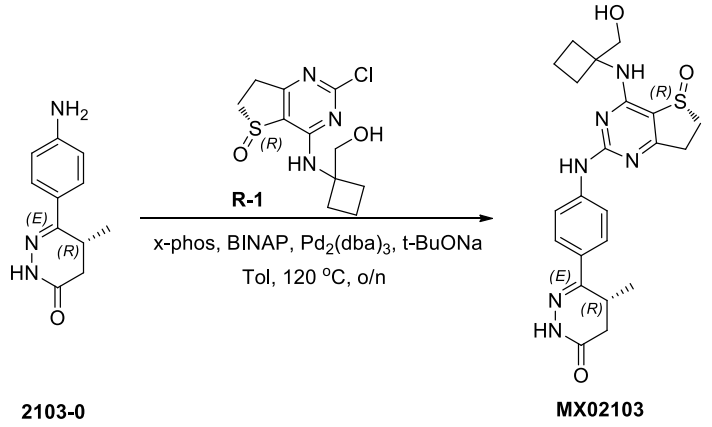
MX02103

1. Synthetic scheme:



2. Experimental section:

2.1(*R*)-6-(4-(((*R*)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)amino)phenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (MX02103)

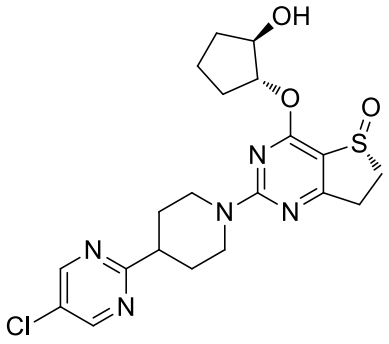


To a solution of compound (*R*)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2*H*)-one (100 mg, 0.49 mmol) in toluene (4 mL) were added (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (141 mg, 0.49 mmol), X-phos (10 mg, 0.02 mmol), BINAP (12 mg, 0.02 mmol), *t*-BuONa (94 mg, 0.98 mmol) and $Pd_2(dba)_3$ (18 mg, 0.02 mmol). The resulted reaction mixture was stirred at 120 °C overnight under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (6.84 mg, 3% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{22}H_{26}N_6O_3S]$ $[M+H]^+$: 455.2; found: 455.0

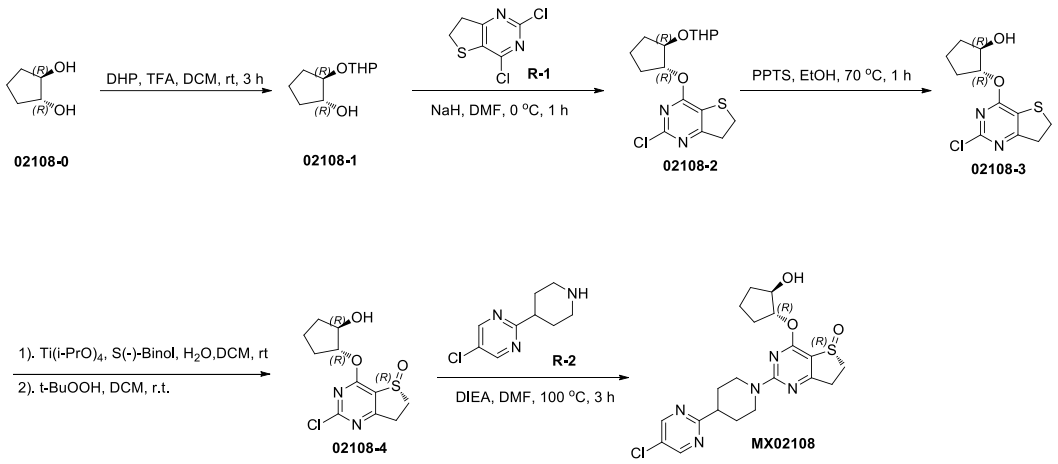
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 9.71 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H),7.59 (s, 1H), 4.87 (t, *J* = 5.2 Hz, 1H), 3.83 – 3.76 (m, 2H), 3.53 – 3.47

(m, 1H), 3.45 – 3.37 (m, 1H), 3.29 – 3.24 (m, 1H), 3.04 – 2.98 (m, 1H), 2.95 – 2.90 (m, 1H), 2.70 – 2.65 (m, 1H), 2.45 – 2.20 (m, 5H), 1.83 – 1.74 (m, 2H), 1.07 (d, *J* = 7.2 Hz, 3H) .



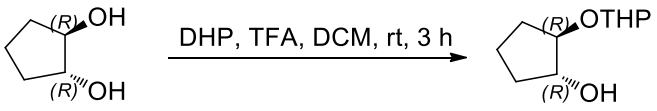
MX02108

1. Synthetic scheme:



2. Experimental section:

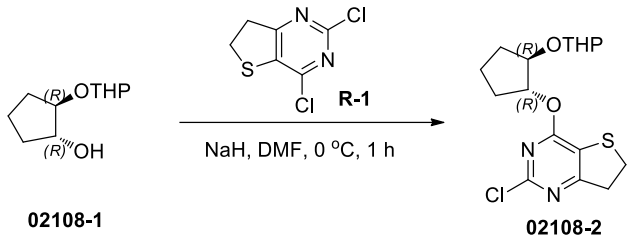
2.1 (1*R*,2*R*)-2-((Tetrahydro-2*H*-pyran-2-yl)oxy)cyclopentanol (02108-1)



02108-0 **02108-1**

To a solution of (1*R*,2*R*)-cyclopentane-1,2-diol (2 g, 19.61 mmol) in DCM (20 mL) was added DHP (1.65 g, 19.61 mmol) and TFA (0.6 mL). The resulted reaction mixture was stirred at room temperature for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by TLC), the reaction mixture was quenched with water (30 mL). and extracted with DCM (50 mL*3). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title product (3.22 g, 88% yield) as colorless oil, the crude was used to the next step directly.

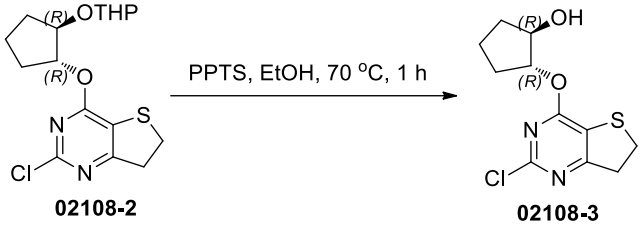
2.22-Chloro-4-(((1*R*,2*R*)-2-((tetrahydro-2*H*-pyran-2-yl)oxy)cyclopentyl)oxy)-6,7-dihydrothieno[3,2-*d*]pyrimidine (02108-2)



To a solution of (1*R*,2*R*)-2-((tetrahydro-2*H*-pyran-2-yl)oxy)cyclopentanol (2 g, 11.11 mmol) in THF (40 mL) was added NaH (60%, 888 mg, 22.22 mmol) at 0°C under N_2, the mixture was stirred at 0°C for 30 minutes, then 2,4-dichloro-6,7-dihydrothieno[3,2-*d*]pyrimidine (2.3 g, 11.11 mmol) was added, the mixture was stirred at 0°C for 1 hour. After the consumption of starting material (monitored by LCMS), the mixture was quenched with water (20 mL) and extracted with EA (50 mL*3). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/1, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to afford the title product (1.12 g, 29% yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{16}H_{21}ClN_2O_3S]$ $[M+H]^+$: 357.1; found: 357.2

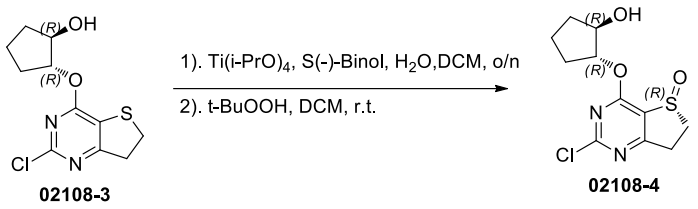
2.3(1*R*,2*R*)-2-((2-Chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)oxy)cyclopentanol (02108-3)



To a solution of 2-chloro-4-(((1*R*,2*R*)-2-((tetrahydro-2*H*-pyran-2-yl)oxy)cyclopentyl)oxy)-6,7-dihydrothieno[3,2-*d*]pyrimidine (1.12 g, 3.15 mmol) in EtOH (10 mL) was added PPTS (15 mg, 0.06 mmol). The resulted reaction mixture was stirred at 70 °C for 1 hour under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water (30 mL) and extracted with EA (30 mL*3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/1, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to afford the title product (640 mg, 75% yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{11}H_{13}ClN_2O_2S]$ $[M+H]^+$: 273.0; found: 273.1

2.4(*R*)-2-Chloro-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)oxy)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (02108-4)

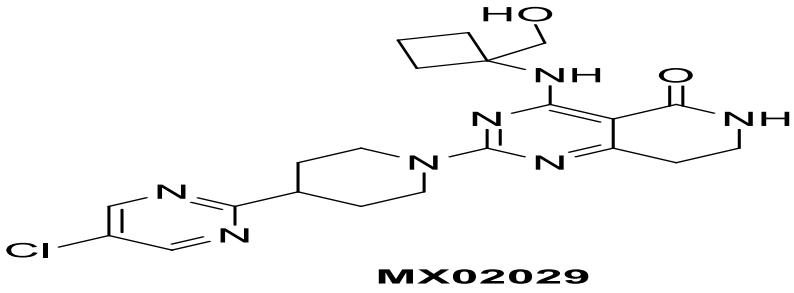


02108-3 02108-4

To a solution of (1*R*,2*R*)-2-((2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)oxy)cyclopentanol (200 mg, 0.73 mmol) and S(-)-Binol (20 mg, 0.07 mmol) in DCM (5 mL) was added $Ti(i\text{-}PrO)_4$ (10 mg 0.036 mmol) and H_2O (13 mg, 0.73 mmol) . The mixture was stirred overnight at room temperature. *t*-BuOOH (70% in water) (131 mg, 1.46 mmol) was added at once, then the mixture was stirred for 1.5 hours at room temperature. Water (20 mL) was added and the mixture was extracted with DCM (50 mL*3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (DCM/MeOH = 1/0~20/1, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to afford the title product (61 mg, 29% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{11}H_{13}ClN_2O_3S]$ $[M+H]^+$: 289.0; found: 289.1

2.5(*R*)-2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)oxy)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02108)

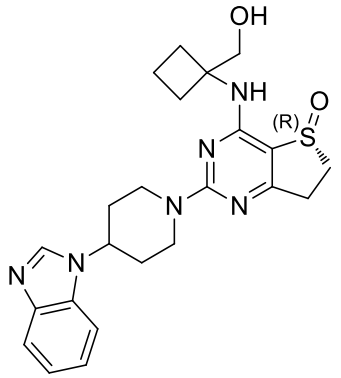


MX02029

To a solution of (*R*)-2-chloro-4-(((1*R*,2*R*)-2-hydroxycyclopentyl)oxy)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (61 mg, 0.21 mmol) in DMF (4 mL) were added 5-chloro-2-(piperidin-4-yl)pyrimidine (41 mg, 0.21 mmol) and DIEA (54 mg, 0.42 mmol). The resulted reaction mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (22.76 mg, 24% yield) as a white solid.

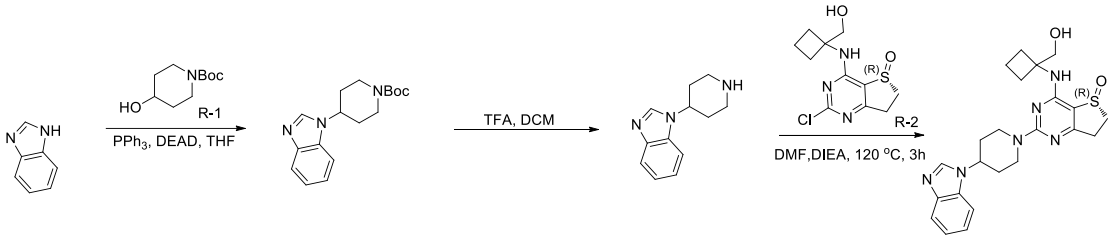
ESI-MS *m/z* calcd for $[C_{20}H_{24}ClN_5O_3S]$ $[M+H]^+$: 450.1; found: 450.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 2H), 5.20 – 5.19 (m, 1H), 5.00 (d, J = 4.0 Hz, 1H), 4.79 (d, J = 13.2 Hz, 2H), 4.14 – 4.10 (m, 1H), 3.57 – 3.48 (m, 1H), 3.31 – 3.16 (m, 4H), 3.10 – 3.04 (m, 1H), 2.96 – 2.91 (m, 1H), 2.20 – 2.13 (m, 1H), 2.07 – 2.04 (m, 2H), 1.88 – 1.81 (m, 1H), 1.76 – 1.51 (m, 6H).



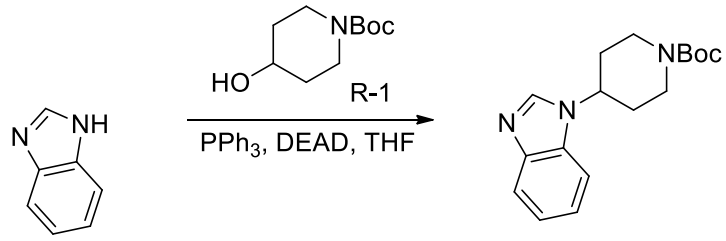
MX02113

1. Synthetic scheme:



2. Experimental section:

2.1 *tert*-Butyl 4-(1*H*-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (02113-1)



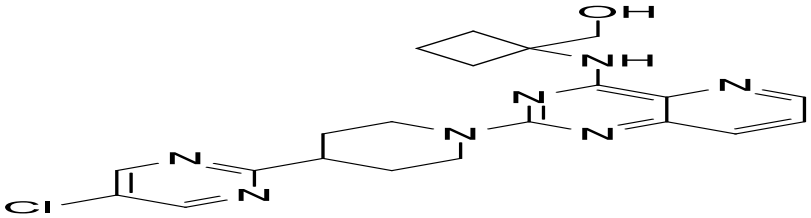
02113-0 **02113-1**

To solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (1.78 g, 9.26 mmol), 1*H*-benzo[*d*]imidazole (4.5 g, 18.52 mmol) and PPh_3 (8.09 g, 18.52 mmol) in anhydrous THF (375 mL) was slowly added DEAD (3.22 g, 18.52mmol) in 250 mL of THF. The reaction mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure The

crude product was purified by column chromatography (EA/PE = 0~100%, Silica-CS 80 g, 80 mL/min, silica gel, UV 254) to obtain product (266 mg, 4.77% yield) as a white soild .

ESI-MS *m/z* calcd for $[C_{17}H_{23}N_3O_2]$ $[M+H]^+$: 302.2; found: 302.2

2.2 1-(Piperidin-4-yl)-1*H*-benzo[*d*]imidazole (02113-2)

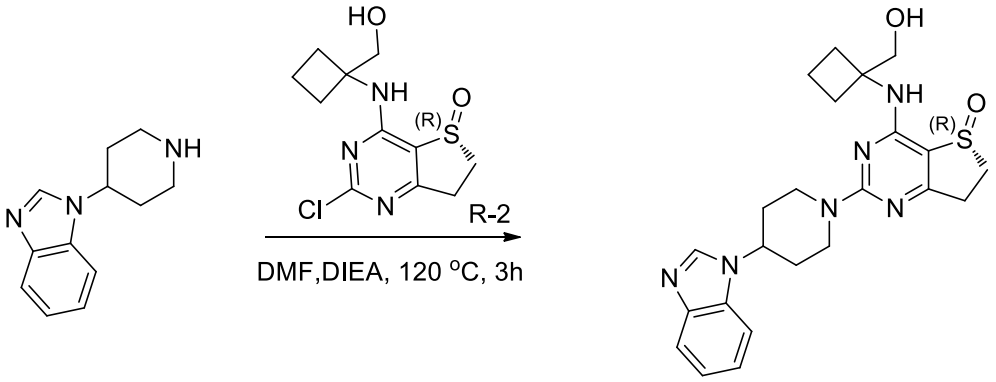


MX02035

To a solution of *tert*-butyl 4-(1*H*-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (240 mg, 0.79 mmol) in THF (2 mL) was added TFA (0.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure and the crude product was used directly in the next step.

ESI-MS *m/z* calcd for $[C_{12}H_{15}N_3]$ $[M+H]^+$: 202.1; found: 202.3

2.3(*R*)-Methyl-2-(4-((2-(4,5-dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-6(7*H*)-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (MX02113)



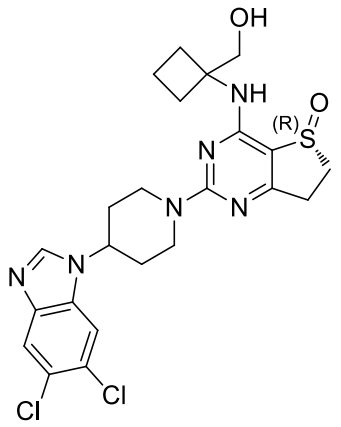
02113-2 MX02113

To a solution of (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (213 mg, 0.74 mmol) and DIEA (286 mg, 2.22 mmol) in DMF (3 mL) was added 1-(piperidin-4-yl)-1*H*-benzo[d]imidazole (purity: 50%, 301 mg, 0.74 mmol). The mixture was stirred for 3 hours at 120 °C. Solvent was removed under reduced pressure. The resiude was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (137.64 mg, 41.1% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{23}H_{28}N_6O_2S]$ $[M+H]^+$: 453.2; found: 453.0

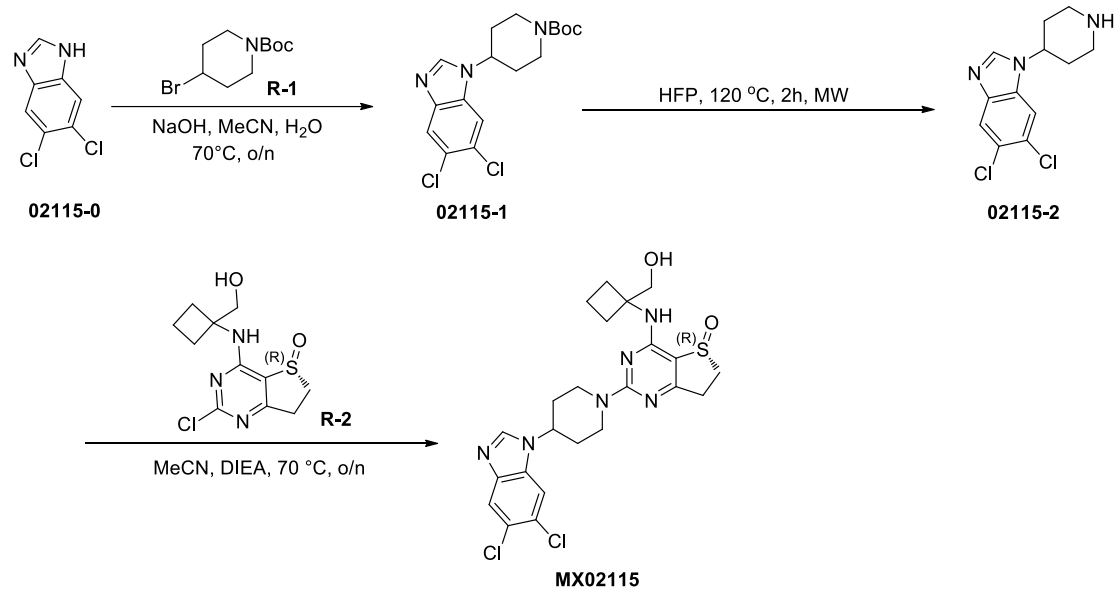
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0

Hz, 1H),7.43 (s, 1H), 7.28 – 7.18 (m, 2H), 4.89 – 4.67 (m, 4H), 3.76 – 3.70 (m, 2H), 3.47– 3.39 (m, 1H), 3.26 – 3.18 (m, 1H), 3.10 (t, *J* = 12.0 Hz, 2H), 2.98 – 2.85 (m, 2H), 2.42 – 2.28 (m, 2H), 2.20 – 2.07 (m, 4H), 1.98 – 1.89 (m, 2H), 1.80 – 1.70 (m, 2H).



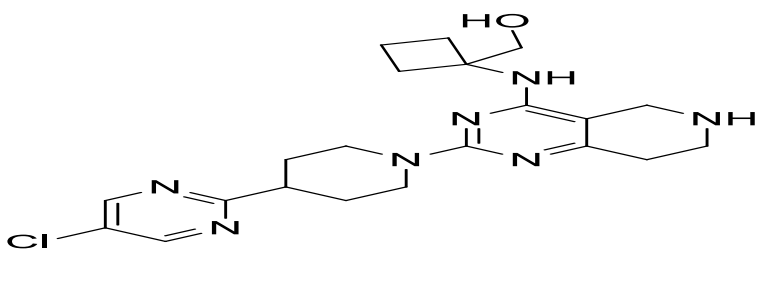
MX02115

1. Synthetic scheme:



2. Experimental section:

2.1 *tert*-Butyl 4-(5,6-dichloro-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carboxylate (02115-1)



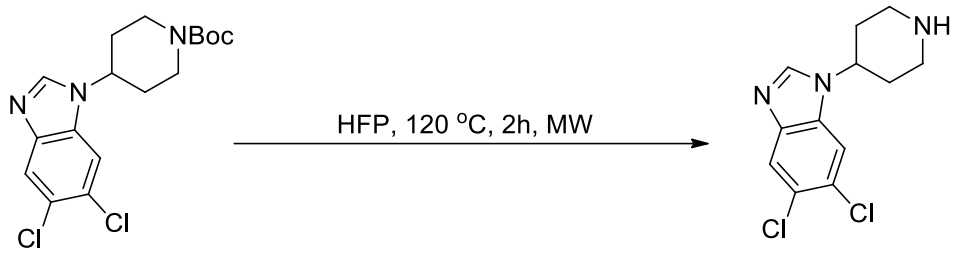
MX02036

To a solution of

5,6-dichloro-1*H*-benzo[*d*]imidazole (600 mg, 3.21 mmol) in MeCN (10.0 mL) and H_2O (4.0 mL) were added *tert*-butyl 4-bromopiperidine-1-carboxylate (1.27 g, 4.81 mmol) and NaOH (642 mg, 16.0 mmol) at room temperature. The reaction mixture was stirred at 70 °C overnight. The reaction mixture was concentrated under reduced pressure and the crude product was extracted by H_2O (30 mL) and DCM (30 mL*3). The organic phase was washed by saturated brine(30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (MeOH/DCM = 0~10%, Silica-CS 20 g, 30 mL/min, silica gel, UV 254) to obtain the title product (128 mg , 10.75% yield) as yellow oil.

ESI-MS *m/z* calcd for $[C_{17}H_{21}Cl_2N_3O_2]$ $[M+H]^+$: 370.1; found: 370.2

2.2 5,6-Dichloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole (02115-2)



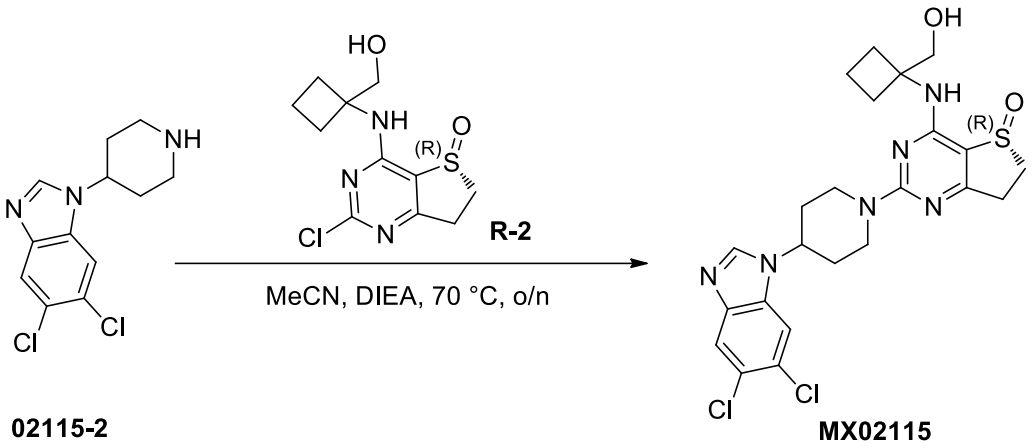
02115-1 **02115-2**

A solution of

tert-butyl 4-(5,6-dichloro-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carboxylate (128.0 mg, 0.347 mmol) and in HFP (2.0 mL) was stirred at 120 °C for 2 hours under microwave condition. The solvent was concentrated under reduced pressure. The crude product was got the crude product (100 mg, 100% yield) used to next step directly as yellow oil.

ESI-MS *m/z* calcd for $[C_{12}H_{13}Cl_2N_3]$ $[M+H]^+$: 270.1; found: 270.1

2.3(*R*)-2-(4-(5,6-Dichloro-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02115)

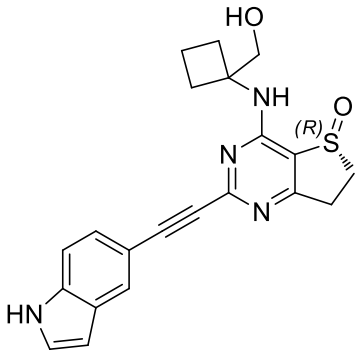


02115-2 **MX02115**

To a solution of 5,6-dichloro-1-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole (100 mg, 0.347 mmol) in MeCN (4.0 mL) were added DIEA (1.0 mL) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (60.0 mg, 0.208 mmol). The mixture was stirred at 70 °C overnight. The solvent was concentrated under reduced pressure. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (39 mg, 45.97% yield) as a white solid.

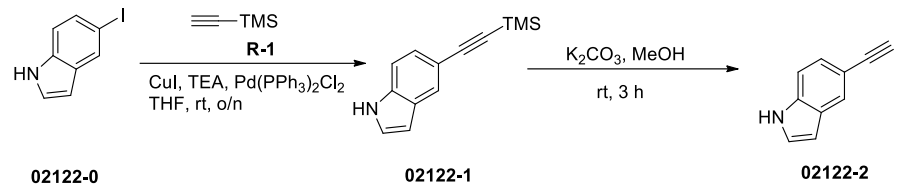
ESI-MS *m/z* calcd for $[C_{23}H_{26}Cl_2N_6O_2S]$ $[M+H]^+$: 521.1; found: 521.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.18 (s, 1H), 7.94 (s, 1H), 7.45 (s, 1H), 4.86 – 4.75 (m, 4H), 3.76 – 3.69 (m, 2H), 3.47 – 3.39 (m, 1H), 3.25 – 3.17 (m, 1H), 3.07 (t, *J* = 12.0 Hz, 2H), 2.98 – 2.85 (m, 2H), 2.41 – 2.28 (m, 2H), 2.19 – 2.14 (m, 2H), 2.11 – 2.08 (m, 2H), 1.94 – 1.86 (m, 2H), 1.80– 1.70 (m, 2H).

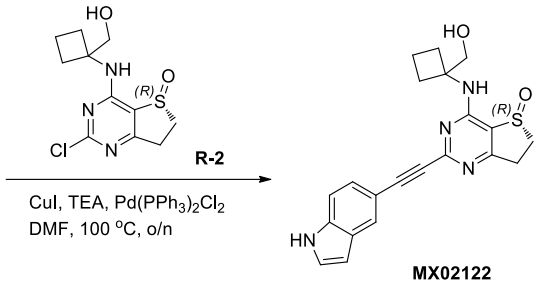


MX02122

1. Synthetic scheme:



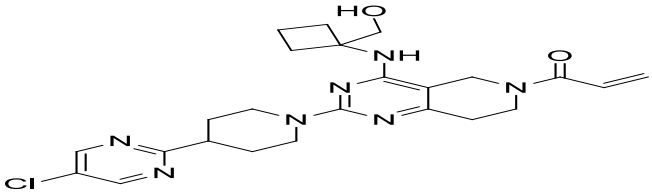
02122-0 02122-1 02122-2



MX02122

2. Experimental section:

2.1 5-((Trimethylsilyl)ethynyl)-1*H*-indole (02122-1)

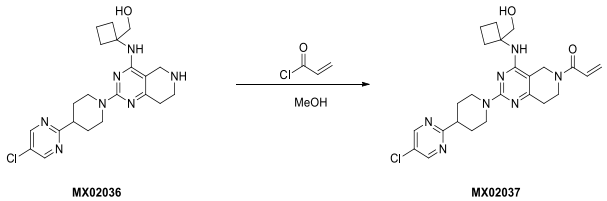


MX02037

To a solution of 5-iodo-1*H*-indole (1 g, 4.11 mmol) in THF (10 mL) were added ethynyltrimethylsilane (444 mg, 4.53 mmol), CuI (78 mg, 0.41 mmol), TEA (5 mL) and $Pd(PPh_3)_2Cl_2$ (84 mg, 0.12 mmol). The resulted reaction mixture was stirred at room temperature overnight under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/10, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to afford the title product (810 mg, 93% yield) as a brown solid.

ESI-MS *m/z* calcd for $[C_{13}H_{15}NSi]$ $[M+H]^+$: 214.1; found: 214.3

2.2 5-Ethynyl-1*H*-indole (02122-2)



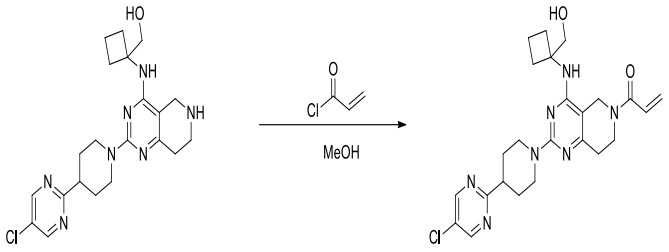
MX02036 MX02037

To a solution of 5-((trimethylsilyl)ethynyl)-1*H*-indole (810 mg, 3.80 mmol) in MeOH (10 mL) was added K_2CO_3 (787 mg, 5.70 mmol). The resulted reaction mixture was stirred at room temperature for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was filtered and concentrated to afford the title

product (525 mg, 98% yield) as a brown solid.

ESI-MS *m/z* calcd for $[C_{10}H_7N]$ $[M+H]^+$: 142.1; found: 142.0

2.3(*R*)-2-((1*H*-Indol-5-yl)ethynyl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (MX02122)

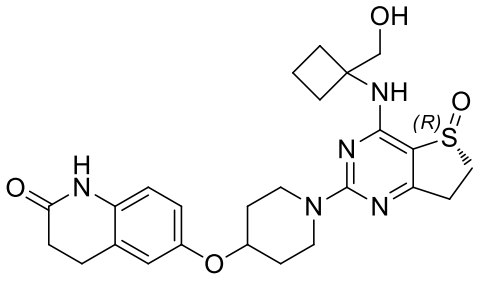


MX02036 MX02037

To a solution of 5-ethynyl-1*H*-indole (100 mg, 0.71 mmol) in DMF (5 mL) were added (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (204 mg, 0.71 mmol), CuI (13 mg, 0.07 mmol), TEA (143 mg, 1.42 mmol) and $Pd(PPh_3)_2Cl_2$ (34 mg, 0.05 mmol). The resulted reaction mixture was stirred at 100 °C overnight under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water (20 mL)and extracted with EA (30 mL*3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (25.61 mg, 9% yield) as a white solid.

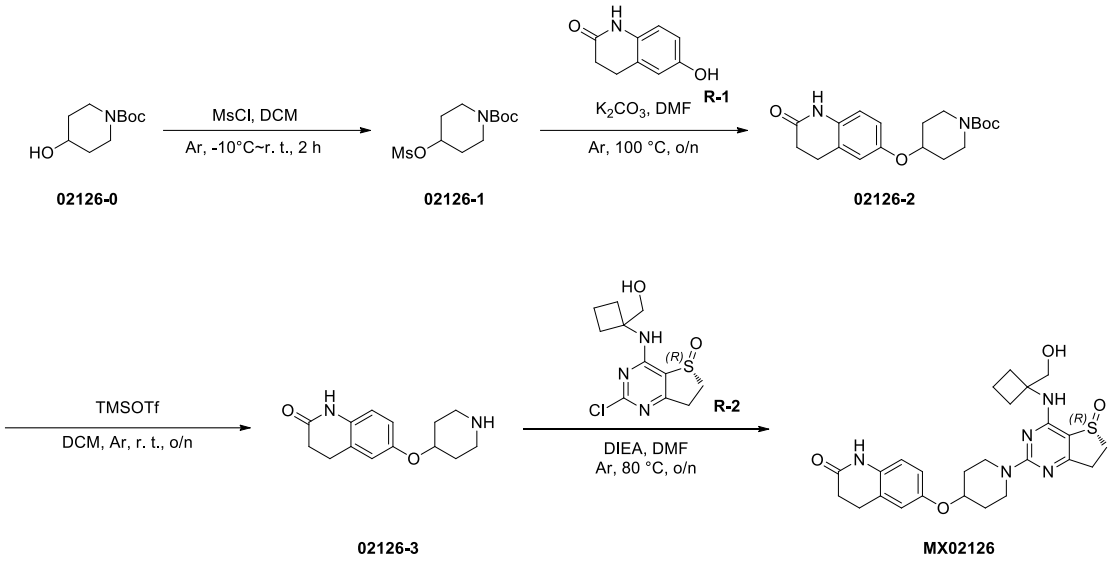
ESI-MS *m/z* calcd for $[C_{21}H_{20}N_4O_2S]$ $[M+H]^+$: 393.1; found: 393.0

^{1}H NMR (400 MHz, DMSO-d_6) δ11.45 (s, 1H), 8.11 (s, 1H), 7.87 (s, 1H), 7.48 – 7.46 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.51 (s, 1H), 4.93 (t, *J* = 5.6 Hz, 1H), 3.80 – 3.72 (m, 2H), 3.62 – 3.53 (m, 1H), 3.38 – 3.31 (m, 1H), 3.18 – 3.14 (m, 1H), 3.04 – 2.99 (m, 1H), 2.38 – 2.25 (m, 4H), 1.83 – 1.74 (m, 2H).



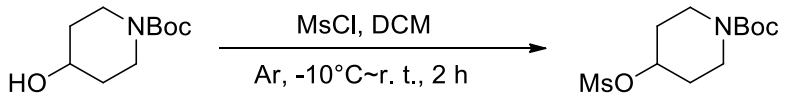
MX02126

1. Synthetic scheme:



2. Experimental section:

2.1 *tert*-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (02126-1)

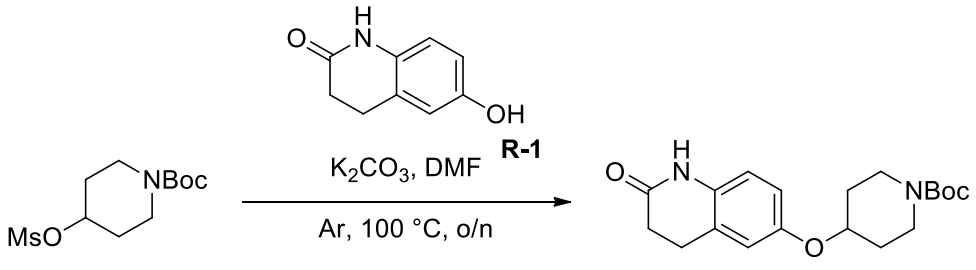


02126-0 **02126-1**

To a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (1.0 g, 5.0 mmol) and TEA (1.4 mL, 10.0 mmol) in DCM (15 mL) was added MsCl (0.43 g, 5.5 mmol) in DCM (5 mL) dropwise over 15 minutes at -10 ºC. After addition was completed, The reaction was warmed to room temperature and stirring for 2 hours. The mixture was quenched with 1N HCl (20 mL). The organic phase was washed with 1N HCl (20 mL), saturated brine (10 mL), 1N NaOH (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude title product (1.38 g, 99.4 % yield) as a pale pink solid.

ESI-MS *m/z* calcd for $[C_{11}H_{21}NO_5S]$ $[M-56+H]^+$: 224.1; found: 224.2

2.2*tert*-Butyl-4-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy)piperidine-1-carboxylate (02126-2)



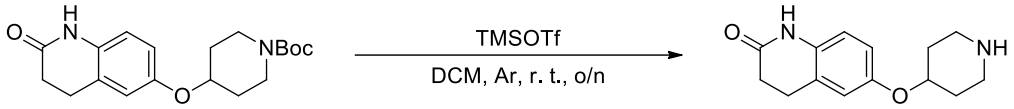
02126-1 **02126-2**

A mixture of *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (257 mg, 0.92

mmol), 6-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (100 mg, 0.61 mmol) and K_2CO_3 (101 mg, 0.73 mmol) in DMF (20 mL) was stirred at 100 ºC overnight under argon. After cooling, the reaction mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0~11/9, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give crude product (100 mg) and then the crude prouduct was purified by reversed-phase chromatography (MeCN/H_2O =1/9 ~ 9/11, C-18 column, 50 mL/min, UV 214) to give the title product (41 mg, 19.3 % yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{19}H_{26}N_2O_4]$ $[M-56+H]^+$: 291.2; found: 291.0

2.3 6-(Piperidin-4-yloxy)-3,4-dihydroquinolin-2(1*H*)-one (02126-3)

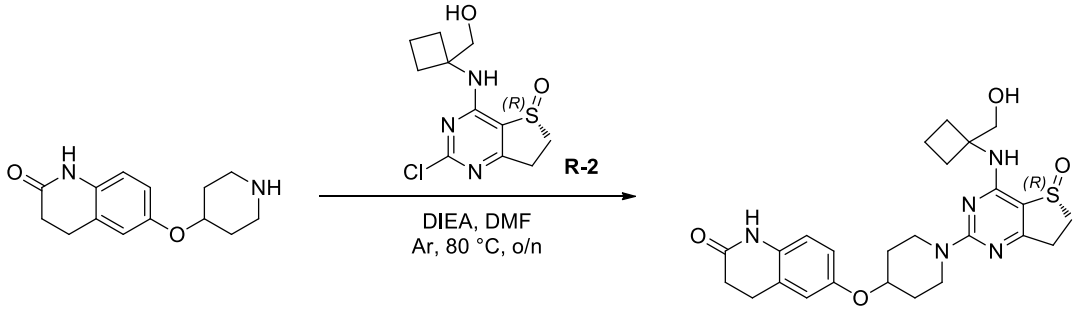


02126-2 **02126-3**

To a solution of *tert*-butyl 4-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy)piperidine-1-carboxylate (20 mg, 0.058 mmol) in DCM (5 mL) was added TMSOTf (0.015 mL, 0.087 mmol) and then the mixture was stirred at room temperature overnight under argon. Solvent was removed under reduced pressureThe crude product was washed with anhydrous Et_2O (5 mL*3) to remove any soluble side products. The crude product was triturated with DCM (5 mL)to obtain a pale yellow precipitate which was filtered and washed with diethyl ether to give the title product (14 mg, 98.5 % yield) as a pale yellow solid.

ESI-MS *m/z* calcd for $[C_{14}H_{18}N_2O_2]$ $[M+H]^+$: 247.1; found: 247.1

2.4(*R*)-6-((1-(4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-2-yl)piperidin-4-yl)oxy)-3,4-dihydroquinolin-2(1*H*)-one (MX02126)



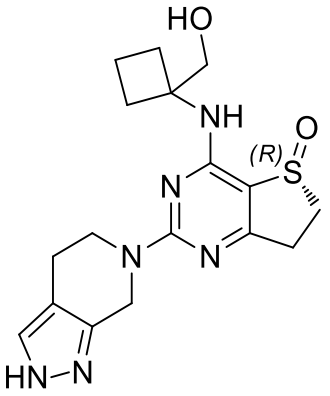
02126-3 **MX02126**

To a solution of 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1*H*)-one (14 mg, 0.06 mmol) and (*R*)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-*d*]pyrimidine 5-oxide (17 mg, 0.06 mmol) in DMF (10 mL) was added DIEA (0.05 mL, 0.3

mmol) and then the mixture was stirred at 80 ºC overnight under argon. After cooling, the mixture was evaporated under reduce pressure to remove the solvent. The crude product was purified by column chromatography (MeOH/DCM = 0~1/9, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give crude product (20 mg) and then the crude prouduct was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (7.72 mg, 27.3 % yield) as a white solid.

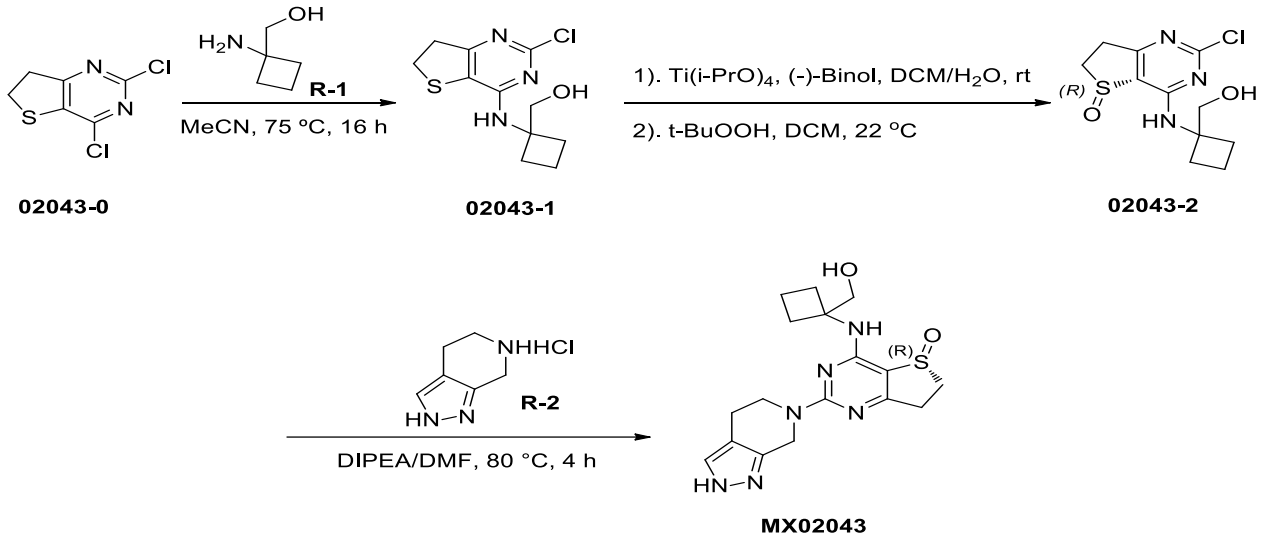
ESI-MS *m/z* calcd for $[C_{25}H_{31}N_5O_4S]$ $[M+H]^+$: 498.2; found: 498.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.41 (s, 1H), 6.85 (s, 1H), 6.80 – 6.74 (m, 2H), 4.85 (t, *J* =5.6 Hz, 1H), 4.55 – 4.51 (m, 1H), 4.16 – 4.12 (m, 2H), 3.73 – 3.68 (m, 2H), 3.53 – 3.36 (m, 3H), 3.23 – 3.16 (m, 1H), 2.95 – 2.81 (m, 4H), 2.42 – 2.38 (m, 2H), 2.35 – 2.24 (m, 2H), 2.17 – 2.13 (m, 2H), 191 – 1.83 (m, 2H), 1.79 – 1.72 (m, 2H), 1.53 – 1.48 (m, 2H).



MX02043

1. Synthetic scheme:

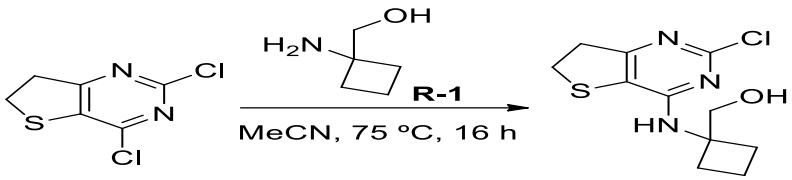


02043-0 02043-1 02043-2

MX02043

2. Experimental section:

2.1 Methyl 2-(2-fluoro-4-nitrophenyl)acetate (02128-1)

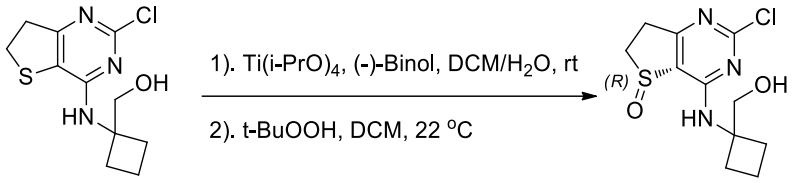


02043-0 02043-1

To a solution of 2-(2-fluoro-4-nitrophenyl)acetic acid (4 g, 20.101 mmol) in MeOH (40 mL) was added conc.H_2SO_4 (2 mL) at room temperature. The reaction mixture was stirred for 4 hours at 80 °C. The reaction mixture was concentrated and the crude product was extracted by aq. $NaHCO_3$ (40 mL) and EA (40 mL*2). The organic phase was washed by saturated brine (40 mL) dried over anhydrous sodium sulfate, filtered and concentrated to obtain product (3.6 g, 84.1% yield) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 – 8.08 (m, 2H), 7.70 (t, J = 8.0 Hz, 1H), 3.94 (s, 2H), 3.66 (s, 3H).

2.2 Methyl 2-(4-amino-2-fluorophenyl)acetate (02128-2)

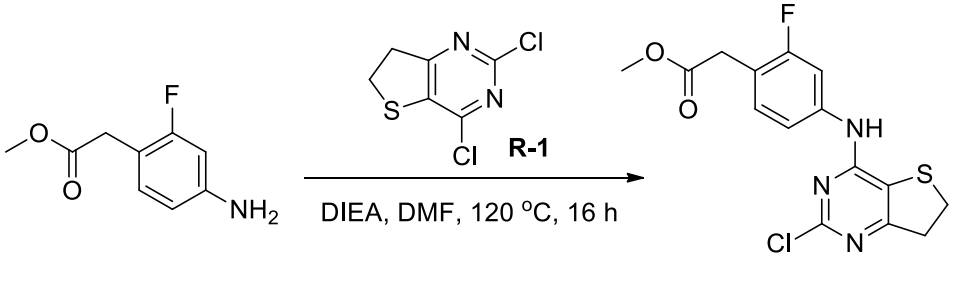


02043-1 02043-2

To a solution of methyl 2-(2-fluoro-4-nitrophenyl)acetate (3.6 g, 16.886 mmol) in EA (40.0 mL) was added a suspension of Pd/C (360 mg) at room temperature. The reaction mixture was stirred overnight under hydrogen atmosphere. After filtered through a celite pad, the solvent was distilled off under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0~4/1, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to obtain product (2.9 g, 93.9% yield) as a yellow solid.

ESI-MS *m/z* calcd for [$C_9H_{10}FNO_2$] $[M+H]^+$: 184.1; found: 184.2

2.3Methyl-2-(4-((2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02128-3)

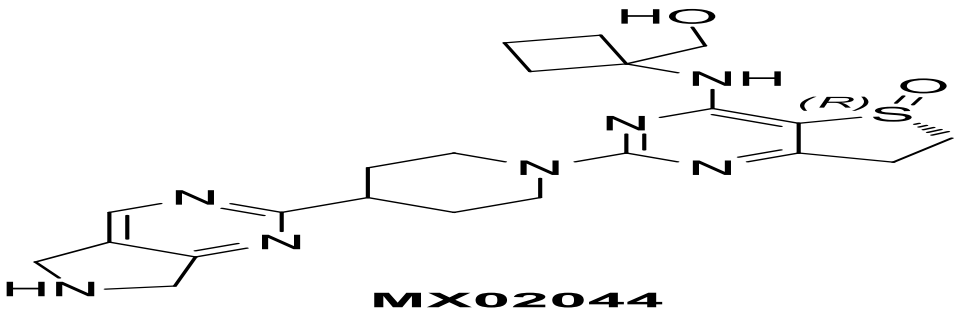


02128-2 02128-3

To a solution of methyl 2-(4-amino-2-fluorophenyl)acetate (3.62 g, 19.76 mmol) and DIEA (7.65 g, 59.279 mmol) in DMF (40 mL) was added 2,4-dichloro-6,7-dihydrothieno[3,2-*d*]pyrimidine (4.09 g, 19.76 mmol). Then the mixture was stirred for 16 hours at 120 °C. The reaction mixture was concentrated and the crude product was extracted by DCM (60 mL*2) and water (60 mL). The combined organic layer was washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (EA/PE = 0/1~1/0, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to afford the title product (1.58 g, 22.6% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{15}H_{13}ClFN_3O_2S]$ $[M+H]^+$: 354.0; found: 354.0

2.4 *(R)*-Methyl 2-(4-((2-chloro-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02128-4)

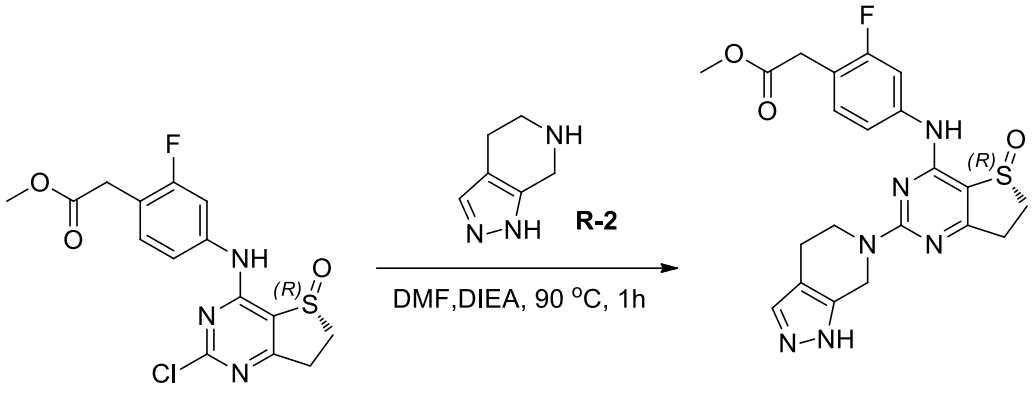


MX02044

To a solution of methyl-2-(4-((2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (500 mg, 1.413 mmol) and *S*(-)-Binol (40.5 mg, 0.141 mmol) in DCM (10 mL) were added $Ti(i\text{-}PrO)_4$ (20.1 mg 0.071 mmol) and H_2O (25.4 mg, 1.413 mmol) . After degassing the flask with three alternating vacuum and nitrogen purge cycles, the mixture was stirred for 1 hour at room temperature under nitrogen atmosphere. *t*-BuOOH (70% in water) (200 mg, 1.555 mmol) was added at once, then the mixture was stirred for 1.5 hours at room temperature under nitrogen atmosphere.Water (20 mL) was added and the mixture was extracted with DCM (60 mL*3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (DCM/MeOH = 1/0~20/1, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give the title product (392 mg, 75.1% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{15}H_{13}ClFN_3O_3S]$ $[M+H]^+$: 370.0; found: 369.9

2.5(*R*)-Methyl-2-(4-((2-(4,5-dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-6(7*H*)-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02128-5)

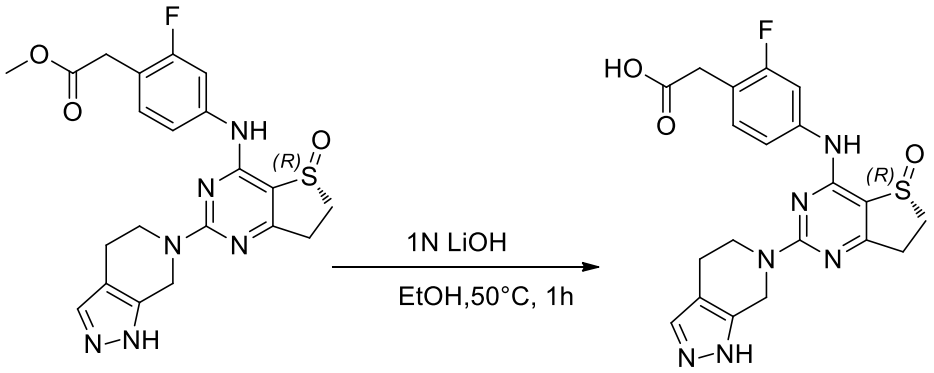


02128-4 **02128-5**

To a solution of (*R*)-methyl-2-(4-((2-chloro-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (60.0 mg, 0.162 mmol) and DIEA (62.8 mg, 0.487 mmol) in DMF (2 mL) was added 4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine (20.0 mg, 0.162 mmol). The mixture was then stirred for 1 hour at 90 °C. The reaction mixture was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (34 mg, 45.9% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{21}H_{21}FN_6O_3S]$ $[M+H]^+$: 457.1; found: 457.0

2.6(*R*)-2-(4-((2-(4,5-Dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-6(7*H*)-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (MX02128)



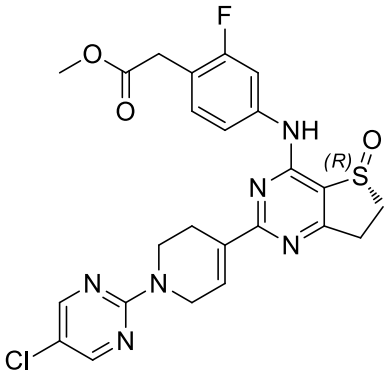
02128-5 **MX02128**

To a solution of (*R*)-Methyl 2-(4-((2-(4,5-dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-6(7*H*)-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (34 mg, 0.074 mmol) in EtOH (2 mL) was added 1N LiOH (0.372 mL, 0.372 mmol). The mixture was then stirred for 1 hour at 50 °C. The pH of the solution was adjusted to 6 with 1N aq. HCl. Solvent was removed under reduced pressure and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to

afford the title product (11.57 mg, 35.1% yield) as a white solid.

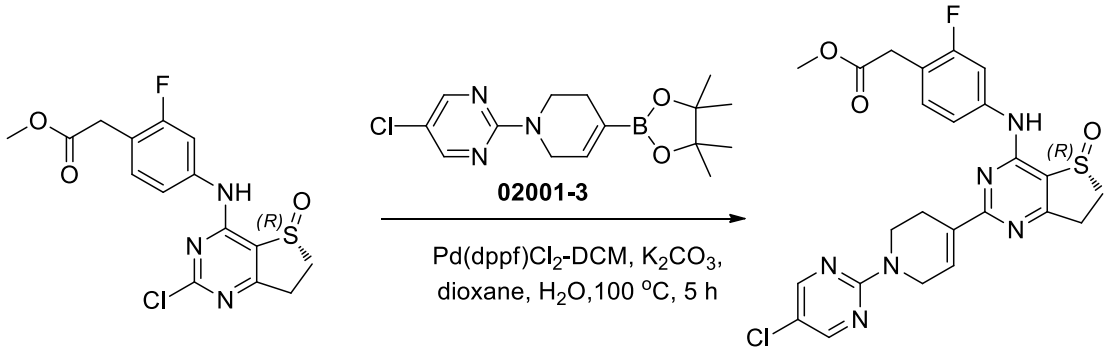
ESI-MS *m/z* calcd for $[C_{20}H_{19}FN_6O_3S]$ $[M+H]^+$: 443.1; found: 443.0

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.52 – 7.49 (m, 1H), 7.40 – 7.36 (m, 2H), 7.30 (t, *J* = 8.4 Hz, 1H), 4.97 (s, 2H), 4.12 – 4.09 (m, 2H), 3.70 – 3.62 (m, 1H), 3.56 (s, 2H), 3.44 – 3.37 (m, 1H), 3.19 – 3.10 (m, 2H), 2.71 (t, *J* = 5.6 Hz, 2H).



MX02129

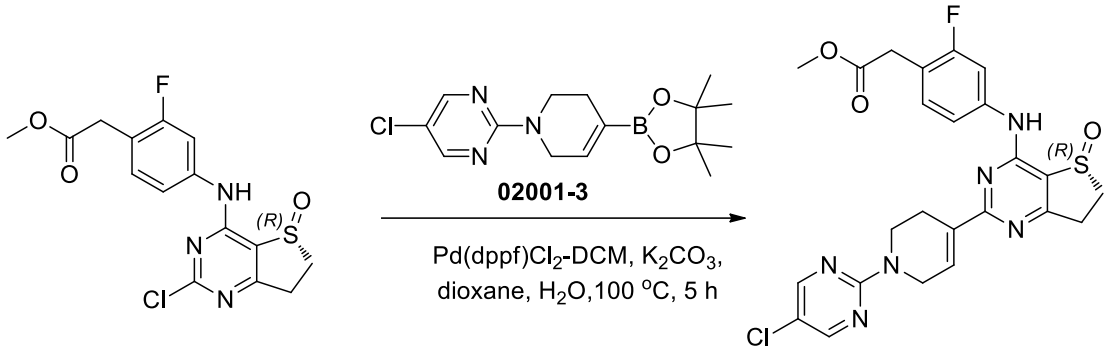
1. Synthetic scheme:



02129-0 **MX02129**

2. Experimental section:

2.1(*R*)-Methyl-2-(4-((2-(1-(5-chloropyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (MX02129)

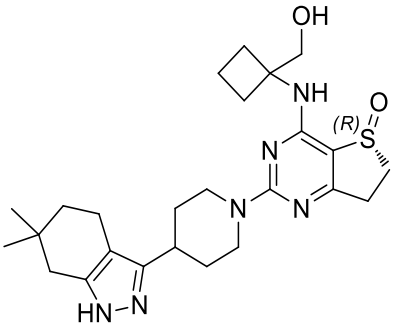


02129-0 **MX02129**

To a solution of (*R*)-methyl 2-(4-((2-chloro-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (332 mg, 0.898 mmol) and 5-chloro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridin-1(2*H*)-yl)pyrimidine (317.6 mg, 0.988 mmol) in 1,4-dioxane/H_2O (10 mL, v/v5:1) were added K_2CO_3 (372.2 mg, 2.693 mmol), $Pd(dppf)Cl_2$ (65.7 mg, 0.090 mmol). After degassing the flask with three alternating vacuum and nitrogen purge cycles, the mixture was stirred for 5 hours at 100 °C under nitrogen atmosphere. Solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (DCM/MeOH = 1/0~20/1, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to give crude product. The crude material was further purified by preparative HPLC [MeCN/H_2O (0.5 % NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (48 mg, 10.1% yield) as a white solid.

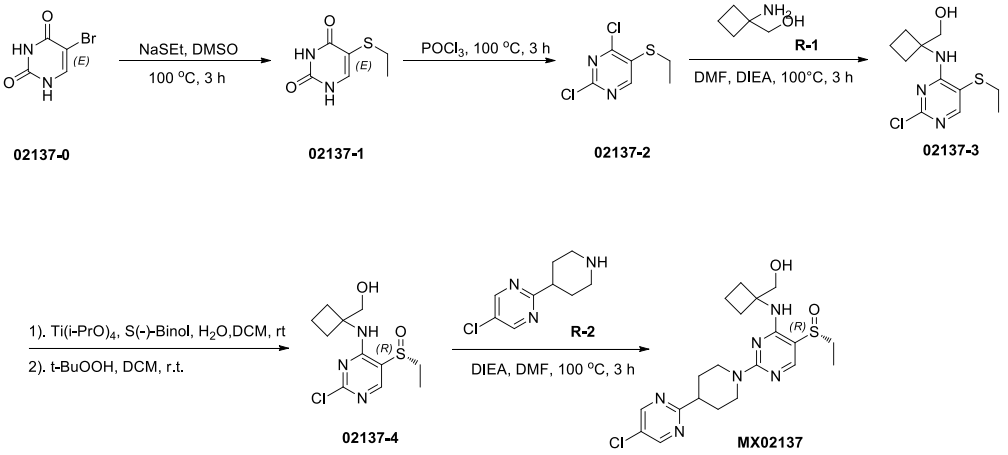
ESI-MS *m/z* calcd for $[C_{24}H_{22}ClFN_6O_3S]$ $[M+H]^+$: 529.1; found: 529.0

^1H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.47 (s, 2H), 7.72 (dd, *J* = 12.4, 2.0 Hz, 1H), 7.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.36 – 7.29 (m, 2H), 4.43 - 4.42 (m, 2H), 3.99 – 3.95 (m, 2H), 3.72 – 3.63 (m, 6H), 3.46 – 3.37 (m, 1H), 3.29 – 3.25 (m, 1H), 3.14 – 3.09 (m, 1H), 2.68 – 2.67 (m, 2H).



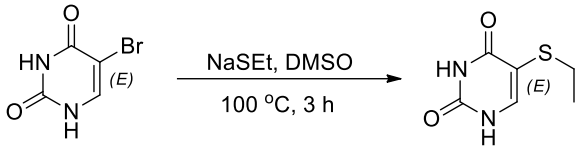
MX02053

1. Synthetic scheme:



2. Experimental section:

2.1 5-(Ethylthio)pyrimidine-2,4(1*H*,3*H*)-dione (02137-1)

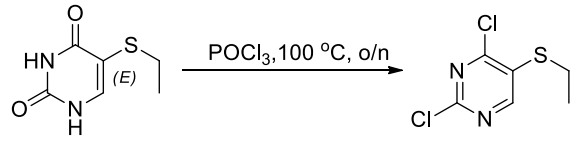


02137-0 **02137-1**

To a solution of 5-bromopyrimidine-2,4(1*H*,3*H*)-dione (1.5 g, 7.85 mmol) in DMSO (10 mL) was added NaSEt (659 mg, 7.85 mmol). The resulted reaction mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water (20 mL) and extracted with EA (50 mL*5). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title product (730 mg, 56% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_6H_8N_2O_2S]$ $[M+H]^+$: 173.0; found: 173.2

2.2 2,4-Dichloro-5-(ethylthio)pyrimidine (02137-2)



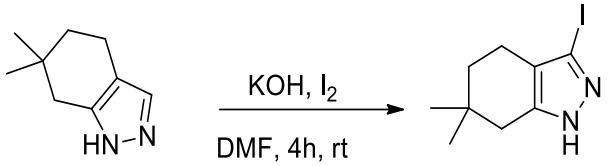
02137-1 **02137-2**

A solution of 5-(ethylthio)pyrimidine-2,4(1*H*,3*H*)-dione (700 mg, 4.07 mmol) in $POCl_3$ (5 mL) was stirred at 100 °C overnight under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water (20 mL) and extracted with EA (40 mL*3). The combined organic layers were washed with saturated brine

(30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/10, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to afford the title product (152 mg, 18% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_6H_6Cl_2N_2S]$ $[M+H]^+$: 209.0; found: 209.0

2.3 (1-((2-Chloro-5-(ethylthio)pyrimidin-4-yl)amino)cyclobutyl)methanol (02137-3)

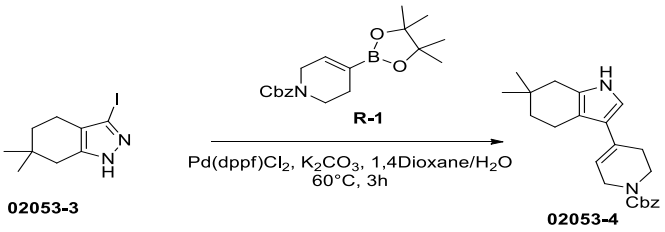


02053-2 **02053-3**

To a solution of 2,4-dichloro-5-(ethylthio)pyrimidine (152 mg, 0.73 mmol) in DMF (3 mL) were added (1-aminocyclobutyl)methanol (76 mg, 0.73 mmol) and DIEA (188 mg, 1.46 mmol), the mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water (20 mL) and extracted with EA (10 mL*3). The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/10, Silica-CS 40 g, 20 mL/min, silica gel, UV 254) to afford the title product (142 mg, 71% yield) as colorless oil.

ESI-MS *m/z* calcd for $[C_{11}H_{16}ClN_3OS]$ $[M+H]^+$: 274.1; found: 274.0

2.4(*R*)-(1-((2-Chloro-5-(ethylsulfinyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (02137-4)



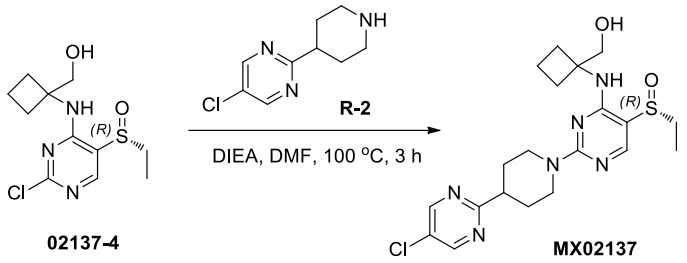
02053-3 **02053-4**

To a solution of (1-((2-chloro-5-(ethylthio)pyrimidin-4-yl)amino)cyclobutyl)methanol (142 mg, 0.52 mmol) and S(-)-Binol (14 mg, 0.05 mmol) in DCM (2 mL) were added Ti(i-PrO)$_4$ (7 mg, 0.026 mmol) and H_2O (9 mg, 0.52 mmol) . The mixture was stirred overnight at room temperature. *t*-BuOOH (70% in water) (94 mg, 1.04 mmol) was added at once, then the mixture was stirred for 1.5 hours at room temperature. Water (20 mL) was added and the mixture was extracted with DCM (50 mL*3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica

gel column chromatography (DCM/MeOH = 1/0~20/1, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to afford the title product (109 mg, 73% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{11}H_{16}ClN_3O_2S]$ $[M+H]^+$: 290.1; found: 290.1

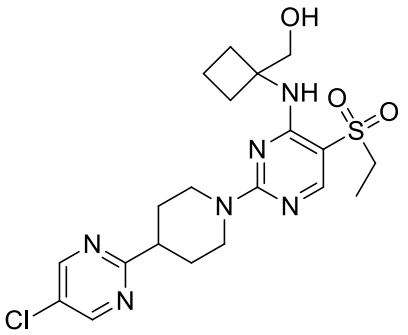
2.5(*R*)-(1-((2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-5-(ethylsulfinyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (MX02137)



To a solution of (*R*)-(1-((2-chloro-5-(ethylsulfinyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (25 mg, 0.08 mmol) in DMF (2 mL) were added 5-chloro-2-(piperidin-4-yl)pyrimidine (20 mg, 0.10 mmol) and DIEA (41 mg, 0.32 mmol). The resulted reaction mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (14.81 mg, 38% yield) as a white solid.

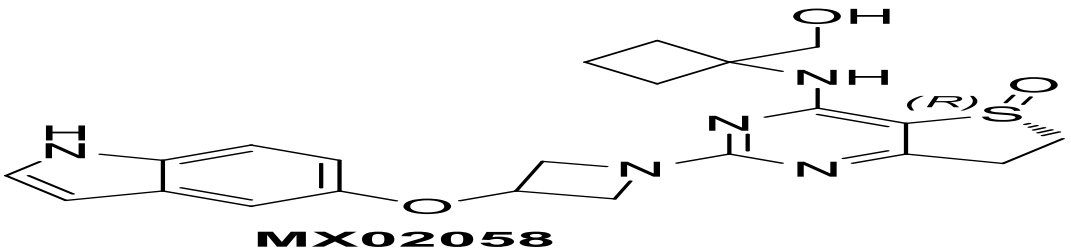
ESI-MS *m/z* calcd for $[C_{20}H_{27}ClN_6O_2S]$ $[M+H]^+$: 451.2; found: 451.5

^{1}H NMR (400 MHz, DMSO-d_6) δ8.87 (s, 2H), 7.91 (s, 1H), 7.34 (s, 1H), 4.90 (t, *J* = 5.6 Hz, 1H), 4.67 (d, *J* = 12.8 Hz, 2H), 3.77 – 3.65 (m, 2H), 3.22 – 3.18 (m, 1H), 3.12 – 3.00 (m, 4H), 2.30 – 2.20 (m, 2H), 2.18 – 2.08 (m, 2H), 2.02 – 1.94 (m, 2H), 1.84 – 1.73 (m, 2H), 1.69 – 1.60 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H).



MX02138

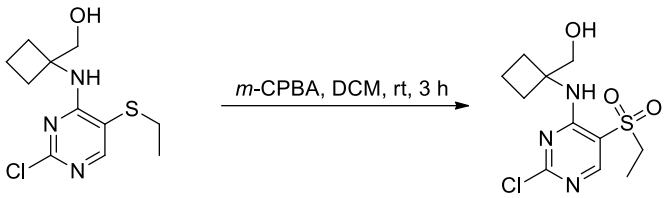
1. Synthetic scheme:



MX02058

2. Experimental section:

2.1(1-((2-Chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (02138-1)

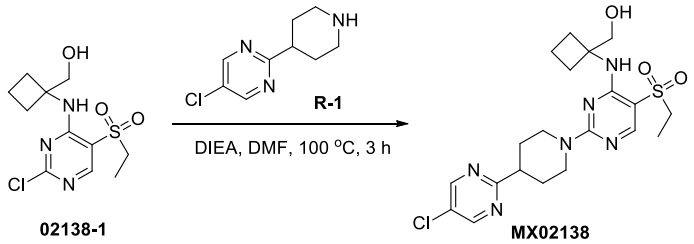


02138-0 02138-1

To a solution of (1-((2-chloro-5-(ethylthio)pyrimidin-4-yl)amino)cyclobutyl)methanol (100 mg, 0.37 mmol) in DCM (5 mL) was added *m*-CPBA (85%, 188 mg, 0.91 mmol). The resulted reaction mixture was stirred at room temperature for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the mixture was quenched with aq.$NaHCO_3$ (10 mL)and extracted with EA (30 mL*3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/4, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to afford the title product (71 mg, 63% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{11}H_{16}ClN_3O_3S]$ $[M+H]^+$: 306.1; found: 306.0

2.2(1-((2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (MX02138)



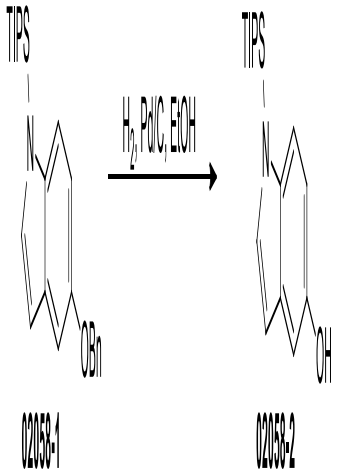
02138-1 MX02138

To a solution of (1-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (71 mg, 0.23 mmol) in DMF (2 mL) were added 5-chloro-2-(piperidin-4-yl)pyrimidine (49 mg, 0.25 mmol) and DIEA (129 mg, 1.00 mmol). The resulted reaction mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. After the consumption

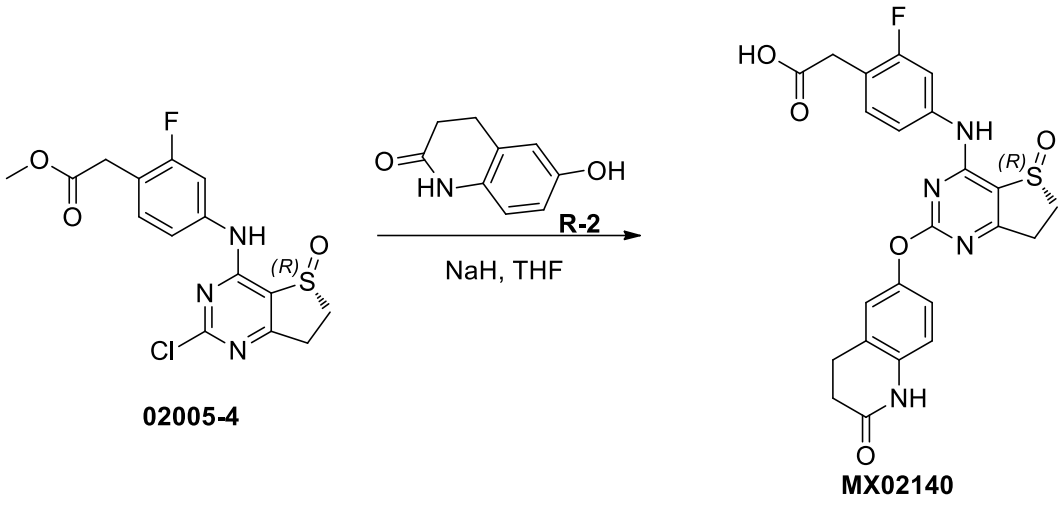
of starting material (monitored by LCMS), the reaction mixture was concentrated. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (57.19 mg, 53% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_{20}H_{27}ClN_6O_3S]$ $[M+H]^+$: 467.2; found: 467.0

^1H NMR (400 MHz, DMSO-d_6) δ8.88 (s, 2H), 8.17 (s, 1H), 6.94 (s, 1H), 4.94 (t, *J* = 6.0 Hz, 1H), 4.83 – 4.60 (m, 2H), 3.71 (d, *J* = 5.2 Hz, 2H), 3.25 – 3.09 (m, 5H), 2.33 – 2.25 (m, 2H), 2.15 – 2.08 (m, 2H), 2.04 – 2.00 (m, 2H), 1.87 – 1.66 (m, 4H), 1.16 (t, *J* = 7.6 Hz, 3H).



1. Synthetic scheme:

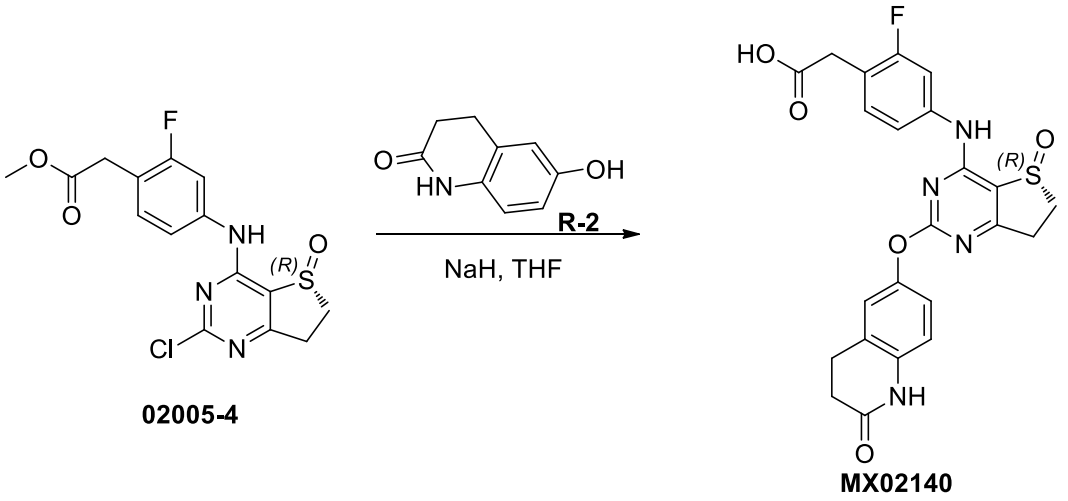


02005-4

MX02140

2. Experimental section:

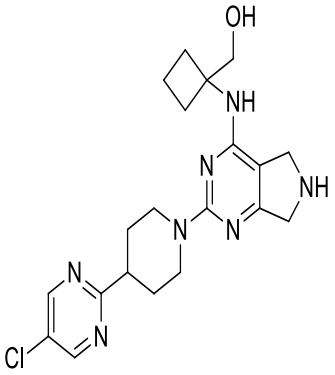
2.1(*R*)-2-(2-fluoro-4-((5-oxido-2-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy)-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)phenyl)acetic acid (MX02140)



To a solution of 6-hydroxy-3,4-dihydroquinolin-2(1H)-one (71 mg, 0.433 mmol) in THF (3 mL) was added NaH (60%, 26 mg, 0.649 mmol) at 0°C. The mixture was stirred at 25 °C for 30 minutes. Then (*R*)-methyl 2-(4-((2-chloro-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (80 mg, 0.216 mmol) was added to the mixture. The mixture was stirred at 25 °C overnight. Water (3 mL) was added. The mixture was stirred at room temperature for 1 hour. The pH of the solution was adjusted to 6 with 1N aq. HCl. The mixture was concentrated. The crude product was purified by reverse-phase column ($MeCN/H_2O$ = 0~20%, C-18, 40 g, 45 mL/min, UV 254) to give crude product (15 mg). The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L HCOOH), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the title product (1.92 mg, 1.84 % yield) as a white solid.

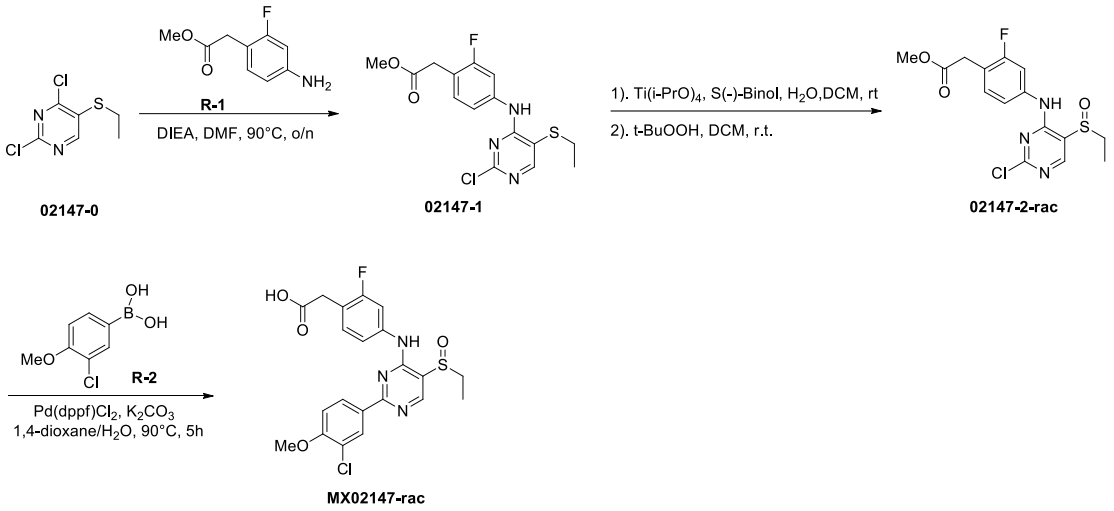
ESI-MS *m/z* calcd for $[C_{23}H_{19}FN_4O_5S]$ $[M+H]^+$: 483.1; found: 483.1

^1H NMR (400 MHz, DMSO-d_6) δ 10.16 – 10.14 (m, 2H), 7.35 (d, *J* = 12.8 Hz, 1H), 7.25 – 7.23 (m, 1H), 7.11 – 7.07 (m, 2H), 6.99 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 3.68 – 3.59 (m, 1H), 3.49 – 3.38 (m, 3H), 3.22 – 3.07 (m, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 2.45 – 2.38 (m, 2H).



MX02060

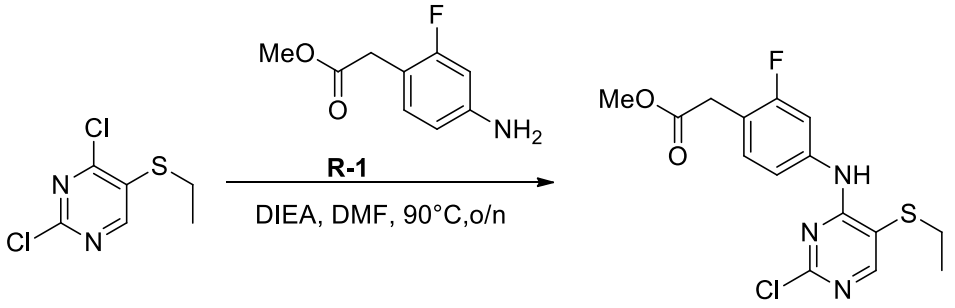
1. Synthetic scheme:



02147-0 02147-1 02147-2-rac MX02147-rac

2. Experimental section:

2.1Methyl-2-(4-((2-chloro-5-(ethylthio)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02147-1)



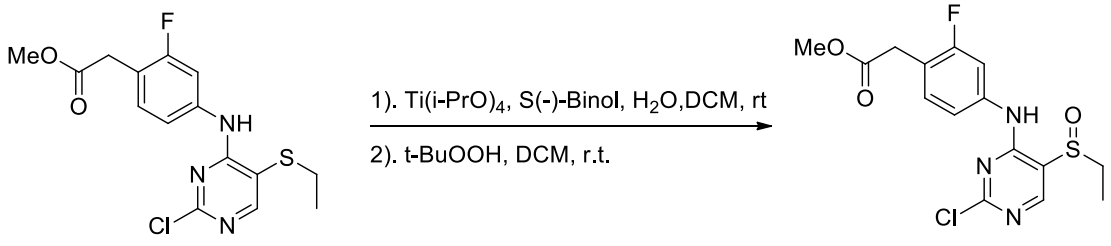
02147-0 02147-1

To a solution of methyl 2-(4-amino-2-fluorophenyl)acetate (272 mg, 1.48 mmol) and DIEA (384 mg, 2.97 mmol) in DMF (10 mL) was added 2,4-dichloro-5-(ethylthio)pyrimidine (310 mg, 1.48 mmol). Then the mixture was stirred overnight at 90 °C. The reaction mixture was concentrated and the crude product was extracted by DCM (20 mL*2) and water (20 mL). The combined organic layer was washed with saturated brine (10 mL), dried over anhydrous

sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (EA/PE = 0/1~1/0, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to afford the title product (177 mg, 33.6% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{15}H_{15}ClFN_3O_2S]$ $[M+H]^+$: 356.1; found: 356.0

2.2Methyl-2-(4-((2-chloro-5-(ethylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02147-2)

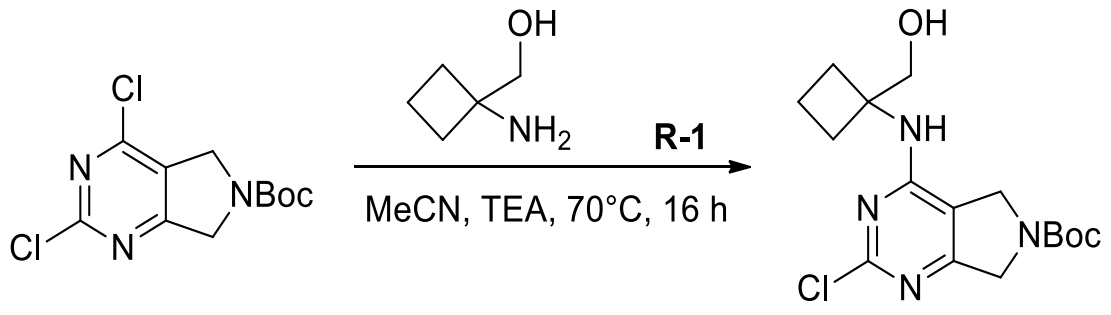


02147-1 02147-2-rac

To a solution of methyl 2-(4-((2-chloro-5-(ethylthio)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (87 mg, 0.245 mmol) and S(-)-Binol (7.0 mg, 0.0245 mmol) in DCM (1.5 mL) were added $Ti(i\text{-}PrO)_4$ (3.5 mg, 0.0123 mmol) and H_2O (4.4 mg, 0.245 mmol). The mixture was stirred for 2 hour at room temperature. *t*-BuOOH (70% in water) (44.2 mg, 0.49 mmol) was added at once, then the mixture was stirred for 3.5 hours at room temperature. Water (5 mL) was added and the mixture was extracted with DCM (10 mL*3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel column chromatography (PE/EA = 1/0~0/1, Silica-CS 12 g, 20 mL/min, silica gel, UV 254) to give the title product (49 mg, 53.8% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{15}H_{15}ClFN_3O_3S]$ $[M+H]^+$: 372.1; found: 372.0

2.32-(4-((2-(3-Chloro-4-methoxyphenyl)-5-(ethylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (MX02147)



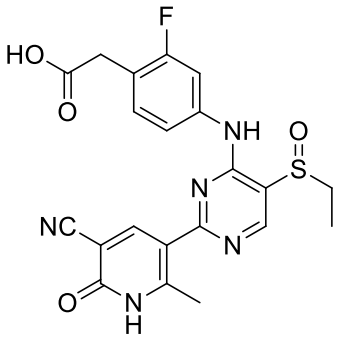
02060-0 02060-1

To a solution of methyl 2-(4-((2-chloro-5-(ethylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (20 mg, 0.054 mmol) and (3-chloro-4-methoxyphenyl)boronic acid (11 mg, 0.06 mmol) in 1,4-dioxane/H_2O (2.5 mL, v/v4:1) were added K_2CO_3 (22.4 mg, 0.162

mmol), $Pd(dppf)Cl_2$ (4.0 mg, 0.0054 mmol). After degassing the flask with three alternating vacuum and nitrogen purge cycles, the mixture was stirred for 5 hours at 100 °C under nitrogen atmosphere. Solvent was removed under reduced pressure, then water (3 mL) was added to the crude product. The pH of the mixture was adjusted to 6 with 1N aq. HCl, then the mixture was extracted with DCM (10 mL*3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L HCOOH), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (2.42 mg, 9.7% yield) as a white solid.

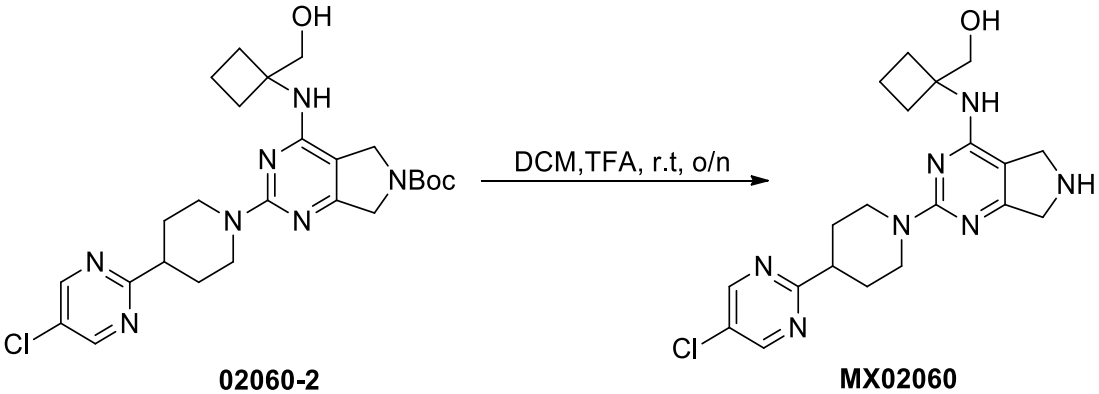
ESI-MS *m/z* calcd for $[C_{21}H_{19}ClFN_3O_4S]$ $[M+H]^+$: 464.1; found: 464.0

^1H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 9.76 (s, 1H), 8.60 (s, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 8.26 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.24 (d, *J* = 12.8 Hz, 1H), 7.37 – 7.33 (m, 3H), 3.95 (s, 3H), 3.64 (s, 2H), 3.23 – 3.16 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H)



MX02148

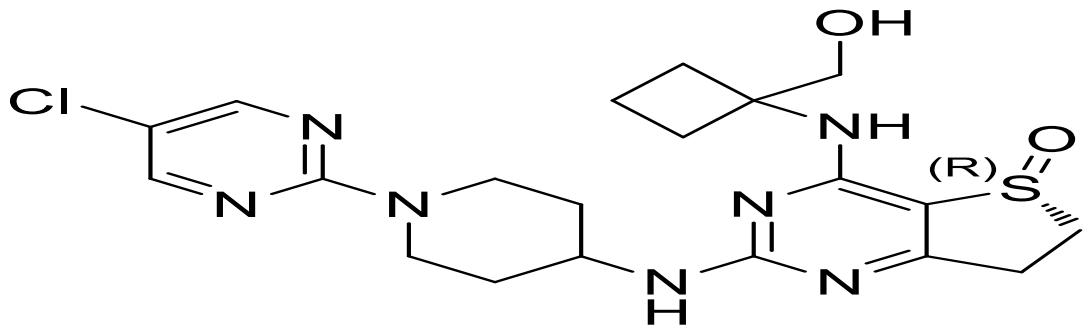
1. Synthetic scheme:



02060-2 **MX02060**

2. Experimental section:

2.12-(4-((2-(5-Cyano-2-methyl-6-oxo-1,6-dihydropyridin-3-yl)-5-(ethylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02148-rac)

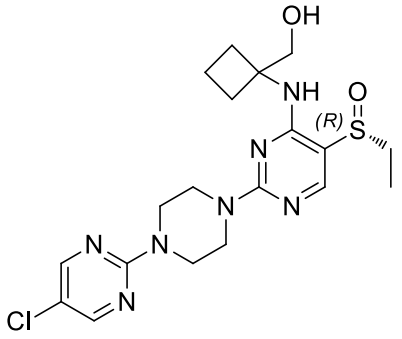


MX02063

To a solution of methyl 2-(4-((2-chloro-5-(ethylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (20 mg, 0.054 mmol) and 6-methyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carbonitrile (15.4 mg, 0.06 mmol) in 1,4-dioxane/H_2O (2.5 mL, v/v4:1) were added K_2CO_3 (22.4 mg, 0.162 mmol), Pd(dppf)Cl_2 (4.0 mg, 0.0054 mmol). After degassing the flask with three alternating vacuum and nitrogen purge cycles, the mixture was stirred for 5 hours at 90 °C under nitrogen atmosphere. Solvent was removed under reduced pressure, then water (5 mL) was added to the crude product. The pH of the mixture was adjusted to 6 with 1N aq. HCl, then the mixture was washed with DCM (5 mL). The layer of water was concentrated to dryness. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L HCOOH), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (5.91 mg, 24.0% yield) as a light green solid.

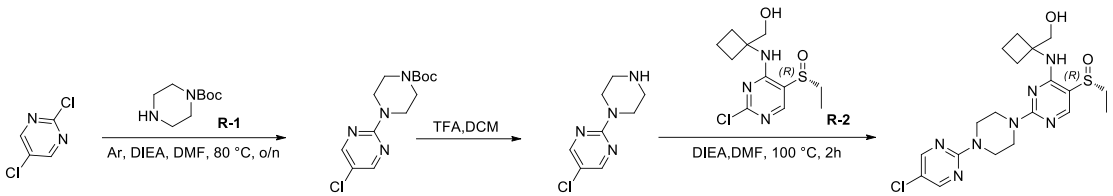
ESI-MS *m/z* calcd for [$C_{21}H_{18}FN_5O_4S$] $[M+H]^+$: 456.1; found: 456.2

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.78 (s, 1H), 8.54 (s, 1H), 7.51 (dd, *J* = 11.6, 2.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.67 (s, 2H), 3.27 – 3.24 (m, 2H), 2.68 (s, 3H) 1.35 (t, *J* = 7.2 Hz, 3H).



MX02149

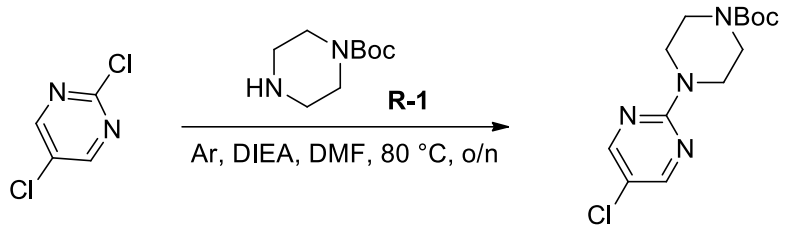
1. Synthetic scheme:



02149-0 02149-1 02149-2 MX02149

2. Experimental section:

2.1 *tert*-Butyl 4-(5-chloropyrimidin-2-yl)piperazine-1-carboxylate (02149-1)

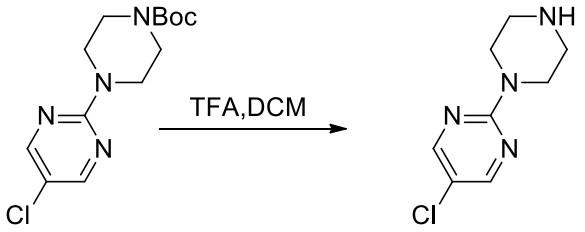


02149-0 02149-1

To a solution of 2,5-dichloropyrimidine (500.0 mg, 3.35 mmol) and DIEA (1.30 g, 10.05 mmol) in DMF (10 mL) was added *tert*-butyl piperazine-1-carboxylate (625.0 mg, 3.35 mmol). The mixture was then stirred overnight at 80 °C, cooled to room temperature and concentrated. The crude product was purified by column chromatography (EA/PE = 0~30%, Silica-CS 40 g, 50 mL/min, silica gel, UV 254) to afford the title product (912 mg, 91.0% yield) as a white solid.

ESI-MS m/z calcd for $[C_{13}H_{19}ClN_4O_2]$ [M-56+H]+: 243.1; found: 243.2

2.2 5-Chloro-2-(piperazin-1-yl)pyrimidine (02149-2)

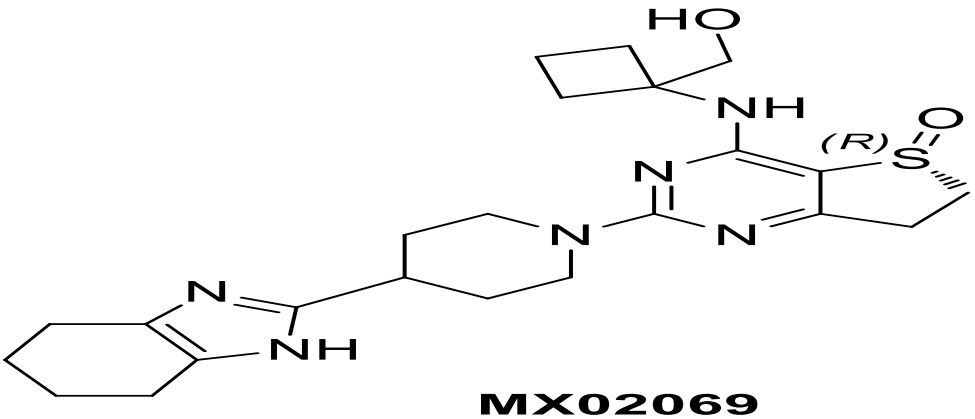


02149-1 02149-2

To a solution of *tert*-butyl 4-(5-chloropyrimidin-2-yl)piperazine-1-carboxylate (50 mg, 0.17 mmol) in DCM (2 mL) was added TFA (0.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure to give the title product (33 mg, 90% yield) was used directly.

ESI-MS *m/z* calcd for $[C_8H_{11}ClN_4]$ $[M+H]^+$:199.1; found: 199.2

2.3(*R*)-(1-((2-(4-(5-Chloropyrimidin-2-yl)piperazin-1-yl)-5-(ethylsulfinyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (MX02149)

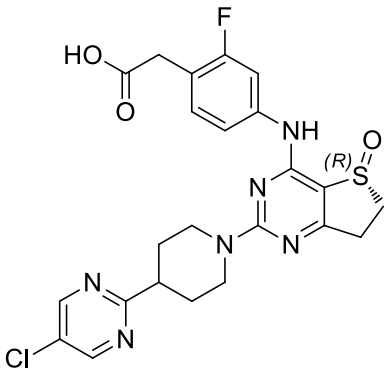


MX02069

To a solution of (*R*)-(1-((2-chloro-5-(ethylsulfinyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (19.0 mg, 0.07 mmol) and DIEA (27.1 mg, 0.21 mmol) in DMF (3 mL) was added 5-chloro-2-(piperazin-1-yl)pyrimidine (13.9 mg, 0.08 mmol). The mixture was then stirred for 2 hours at 100 °C. The reaction mixture was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (27 mg, 72.2%) as an off-white solid.

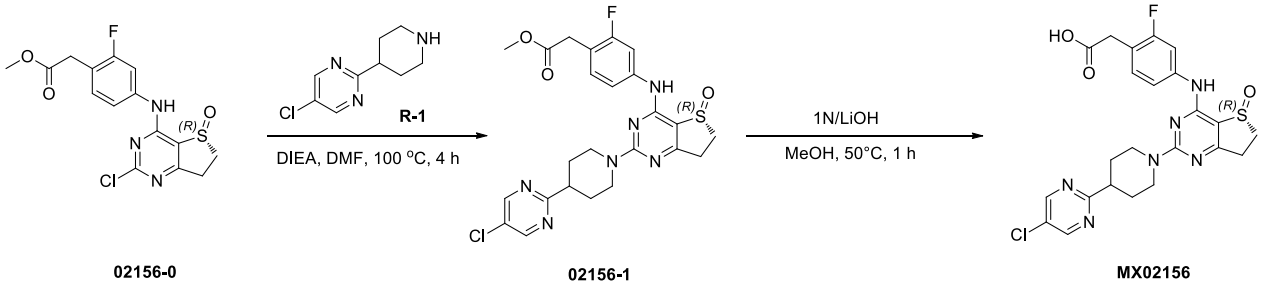
ESI-MS *m/z* calcd for $[C_{19}H_{26}ClN_7O_2S]$ $[M+H]^+$: 452.2; found: 451.9

^1H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 2H), 7.93 (s, 1H), 7.39 (s, 1H), 4.89 (s, 1H), 3.79 – 3.67 (m, 10H), 3.08 – 3.02 (m, 2H), 2.27 – 2.14 (m, 4H), 1.89 – 1.74 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H).



MX02156

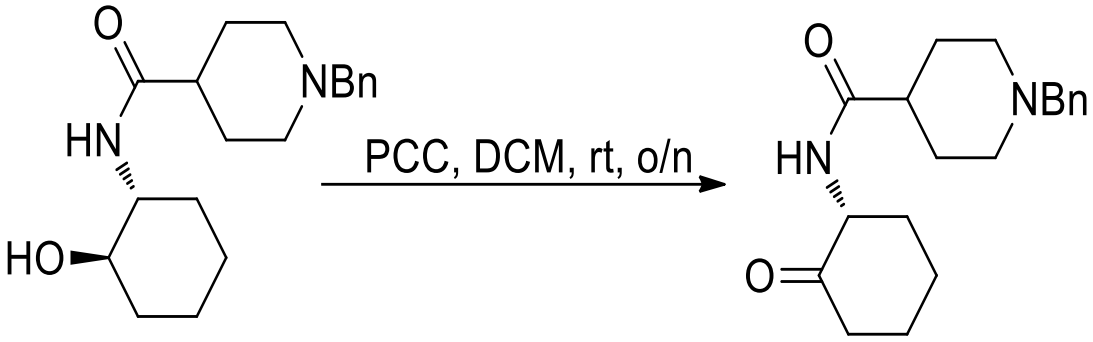
1. Synthetic scheme:



02156-0 **02156-1** **MX02156**

2. Experimental section:

2.1(*R*)-Methyl-2-(4-((2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02115-1)

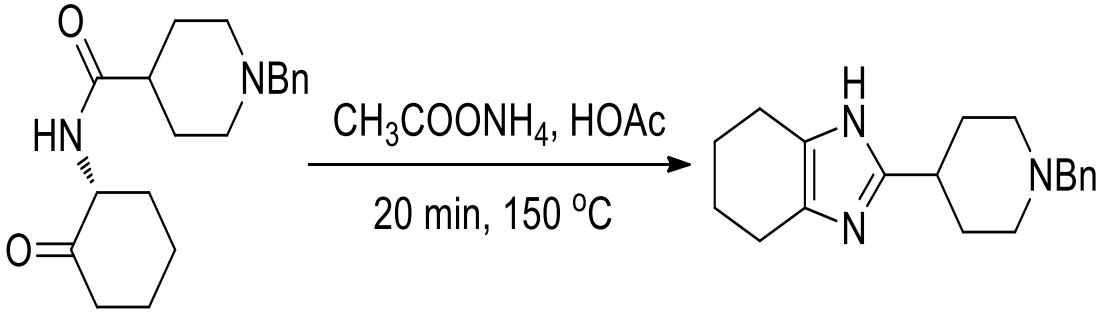


02069-1 **02069-2**

To a solution of 5-chloro-2-(piperidin-4-yl)pyrimidine (40.0 mg, 0.203 mmol) in DMF (4.0 mL) and DIEA (1.0 mL) was added (*R*)-methyl2-(4-((2-chloro-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (50.0 mg, 0.135 mmol). The mixture was stirred for 4 hours at 100 °C. The reaction mixture was concentrated and the crude product was purified by column chromatography (MeOH/DCM = 0~10%, Silica-CS 20 g, 30 mL/min, silica gel, UV 254) to obtain the title product (67.0 mg , 93.0% yield) as a yellow soild.

ESI-MS *m/z* calcd for $[C_{24}H_{24}ClFN_6O_3S]$ $[M+H]^+$: 531.1; found: 531.0

2.2(*R*)-2-(4-((2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-5-oxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (MX02156)



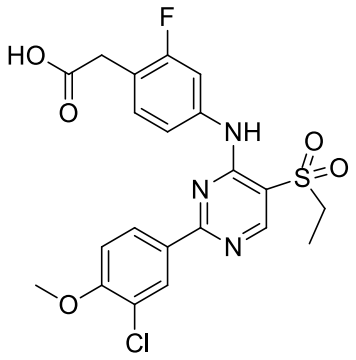
02069-2 **02069-3**

To a solution of ((*R*)-methyl2-(4-((2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-5-oxido-6,7-dihydrothieno [3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (65.0 mg, 0.122 mmol) in MeOH (6.0 mL) was added 1N LiOH (1.22 mL, 1.22 mmol). The mixture was then stirred for 1 hour at 50 °C. The pH of the solution was adjusted to 6 with 1N aq. HCl. Solvent was removed under

reduced pressure and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (28.0 mg, 35.1% yield) as a white solid.

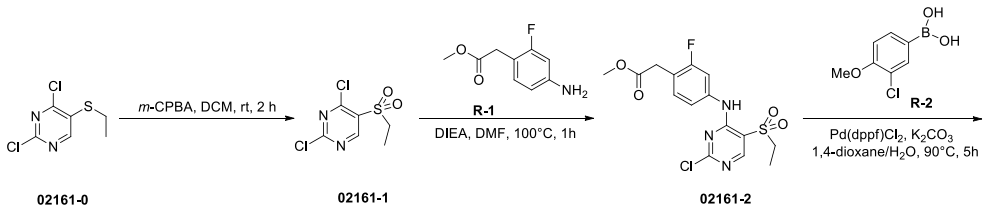
ESI-MS *m/z* calcd for [$C_{23}H_{22}ClFN_6O_3S$] $[M+H]^+$: 517.0; found: 517.0

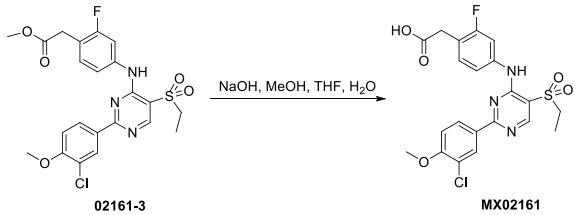
^1H NMR (400 MHz, Methanol-d_4) δ 9.59 (s, 1H), 8.87 (s, 2H), 7.46 (d, J = 12.8 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.16 (t, J = 8.8 Hz, 1H), 4.72 – 4.66 (m, 2H), 3.56 – 3.47 (m, 1H), 3.29 – 2.94 (m, 8H), 2.04 – 2.01 (m, 2H), 1.75 – 1.67 (m, 2H).



MX02161

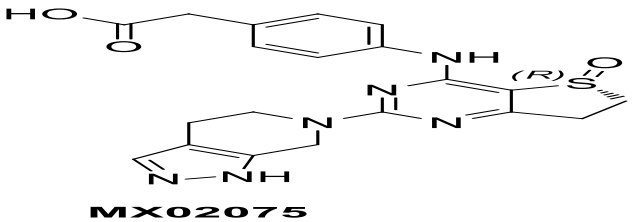
1. Synthetic scheme:





2. Experimental section:

2.1 2,4-Dichloro-5-(ethylsulfonyl)pyrimidine (02161-1)



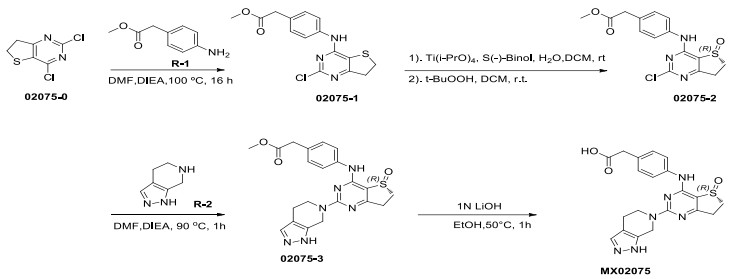
MX02075

To a solution of 2,4-dichloro-5-(ethylthio)pyrimidine (400 mg, 1.92 mmol) in DCM (10 mL) was added *m*-CPBA(85%, 856 mg, 4.22 mmol). The resulted reaction mixture was stirred

at room temperature for 2 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the mixture was quenched with aq. $NaHCO_3$ (20 mL) and extracted with EA (30 mL*3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/4, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to afford the title product (381 mg, 83% yield) as a white solid.

ESI-MS *m/z* calcd for $[C_6H_6Cl_2N_2O_2S]$ $[M+H]^+$: 241.0; found: 241.2

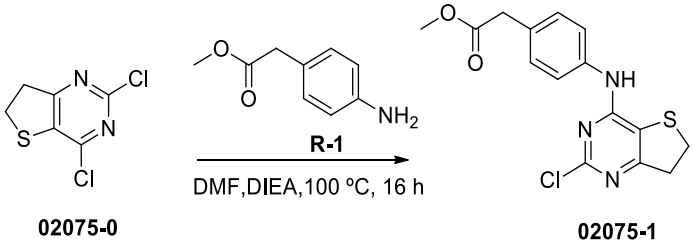
2.2 Methyl 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02161-2)



To a solution of 2,4-dichloro-5-(ethylsulfonyl)pyrimidine (381 mg, 1.58 mmol) in DMF (5 mL) were added methyl 2-(4-amino-2-fluorophenyl)acetate (289 mg, 1.58 mmol) and DIEA (611 mg, 4.74 mmol), the mixture was stirred at 100 °C for 1 hour under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water (20 mL) and extracted with EA (20 mL*3). The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/10, Silica-CS 20 g, 20 mL/min, silica gel, UV 254) to afford the title product (207 mg, 34% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{15}H_{15}ClFN_3O_4S]$ $[M+H]^+$: 388.1; found: 388.0

2.3Methyl-2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02161-3)

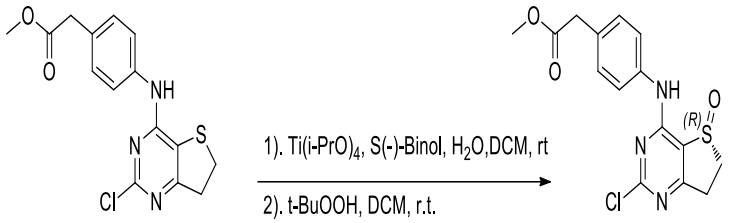


To a solution of methyl 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (100 mg, 0.26 mmol) in 1,4-dioxane/H_2O (2.5 mL, v/v=5/1) were added

(3-chloro-4-methoxyphenyl)boronic acid (58 mg, 0.31 mmol), K_2CO_3 (72 mg, 0.52 mmol) and $Pd(dppf)Cl_2$ (19 mg, 0.026 mmol), the mixture was stirred at 90 °C for 5 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the reaction mixture was quenched with water and extracted with EA (20 mL*3). The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulted crude product was purified by column chromatography on silica gel (EA/PE = 0/1~1/1, Silica-CS 40 g, 40 mL/min, silica gel, UV 254) to afford the title product (51 mg, 40% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{22}H_{21}ClFN_3O_5S]$ $[M+H]^+$: 494.1; found: 493.9

2.42-(4-((2-(3-Chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (MX02161)

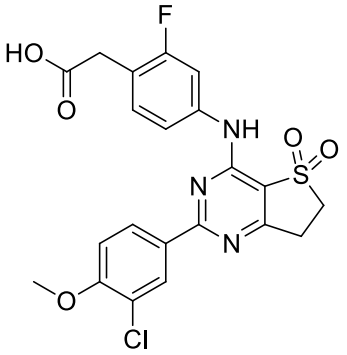


02075-1 02075-2

To a solution of methyl 2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (51 mg, 0.10 mmol) in MeOH/THF (3 mL, v/v=1/1) was added 2N NaOH to adjust the pH of the solution =12. The resulted reaction mixture was stirred at room temperature for 3 hours under N_2 atmosphere. After the consumption of starting material (monitored by LCMS), the pH of the solution was adjusted to 6 with 1N aq. HCl. Then the mixture was concentrated. The resulted crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (6.88 mg, 14% yield) as a white solid.

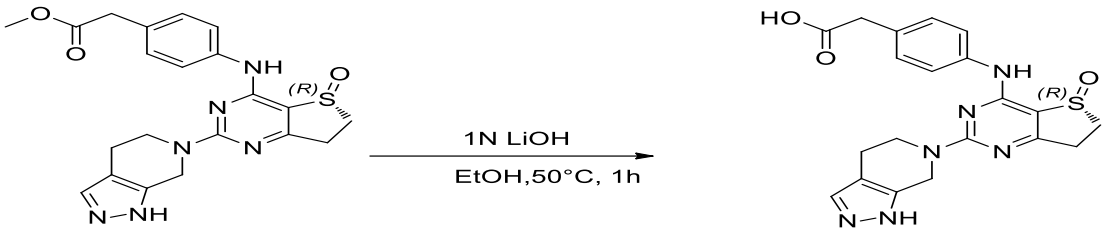
ESI-MS *m/z* calcd for $[C_{21}H_{19}ClFN_3O_5S]$ $[M+H]^+$: 480.1; found: 479.6

^1H NMR (400 MHz, DMSO-d_6+D_2O) δ8.76 (s, 1H), 8.31 (s, 1H), 8.27 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 11.6 Hz, 1H), 7.36 – 7.28 (m, 3H), 3.96 (s, 1H), 3.50 (q, J = 7.2 Hz, 2H), 3.35 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H).



MX02166

1. Synthetic scheme:

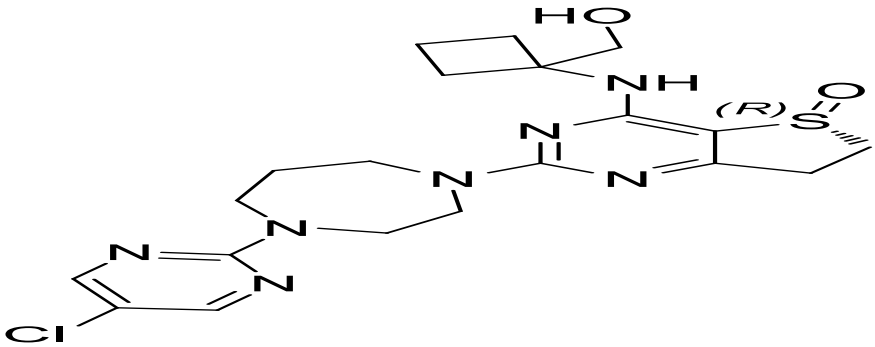


02075-3

MX02075

2. Experimental section:

2.1Methyl-2-(4-((2-Chloro-5,5-dioxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02166-1)

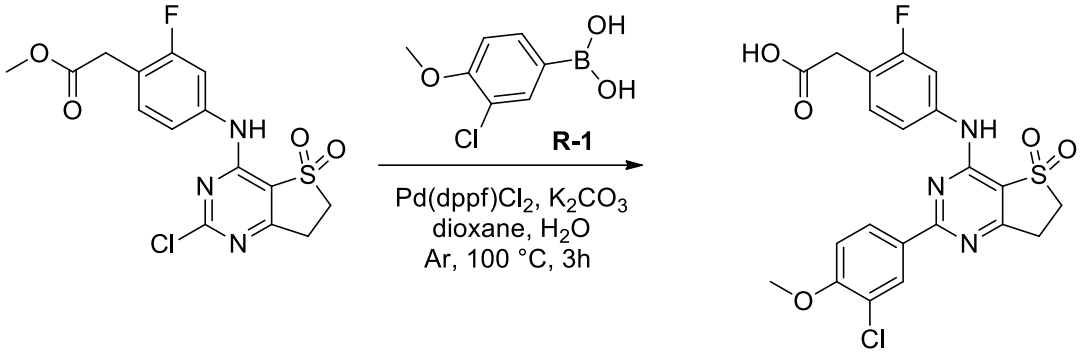


MX02077

To a solution of methyl 2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (200.0 mg, 0.57 mmol) in DCM (10 mL) was added *m*-CPBA (85%, 216.4 mg, 1.25 mmol) at room temperature. The reaction mixture was stirred for 3 hours. The reaction mixture was concentrated and the crude product was extracted by aq. $NaHCO_3$ (40 mL) and EA (40 mL*2). The organic phase was washed by saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (DCM/MeOH = 1/0~20/1, Silica-CS 20 g, 25 mL/min, silica gel, UV 254) to afford the title product (128 mg , 58.7% yield) as a yellow solid.

ESI-MS *m/z* calcd for $[C_{15}H_{13}ClFN_3O_4S]$ $[M+H]^+$: 386.0; found: 385.7

2.22-(4-((2-(3-Chloro-4-methoxyphenyl)-5,5-dioxido-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (MX02166)

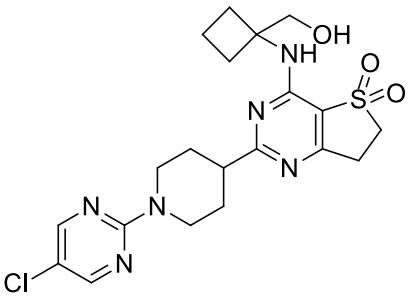


02166-1 **MX02166**

To a solution of methyl 2-(4-((2-chloro-5,5-dioxido-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (70 mg, 0.18 mmol) and 3-chloro-4-methoxyphenyl)boronic acid (33.8 mg, 0.18 mmol) in 1,4-dioxane/H_2O (4.0 mL, v/v 3:1) were added $Pd(dppf)Cl_2$ (14.2 mg, 0.0193 mmol) and K_2CO_3(74.6 mg, 0.54 mmol). After degassing the flask with three alternating vacuum and nitrogen purge cycles, the mixture was stirred for 3 hours at 100 °C under nitrogen atmosphere. Then water (20 mL) was added, the pH of the solution was adjusted to 6 with 1N aq. HCl and the mixture was extracted with EA (20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product which was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the title product (9.16 mg, 9.68% yield) as a white solid.

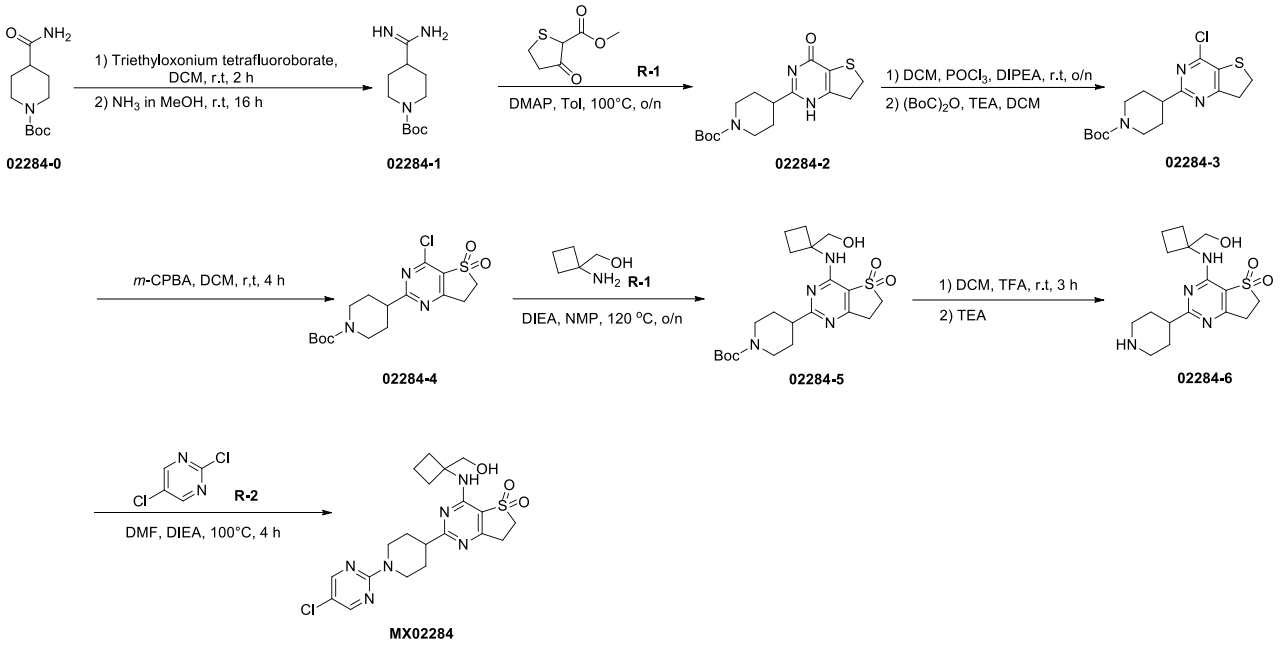
ESI-MS *m/z* calcd for $[C_{21}H_{17}ClFN_3O_5S]$ $[M+H]^+$: 478.1; found: 477.6

^1H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 2.0 Hz, 1H), 8.21 (dd, J = 8.4, 2.0 Hz, 1H), 7.60 (dd, J = 12.0, 2.0 Hz, 1H), 7.48 (dd, J = 8.4, 1.6 Hz, 1H), 7.36 – 7.31 (m, 2H), 3.94 (s, 3H), 3.71 (t, J = 6.8 Hz, 2H), 3.58 (s, 2H), 3.42 – 3.33 (m, 3H).



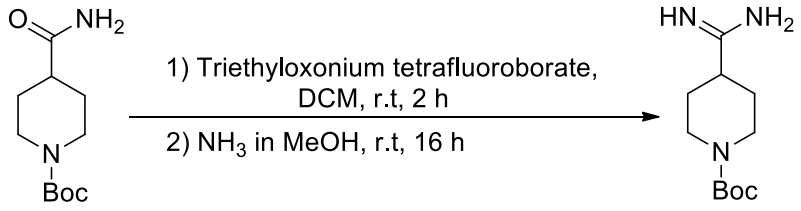
MX02284

1. Synthetic scheme:



2. Experimental section:

2.1 tert-Butyl 4-aminocarbonylpiperidine-1-carboxylate (02284-1)

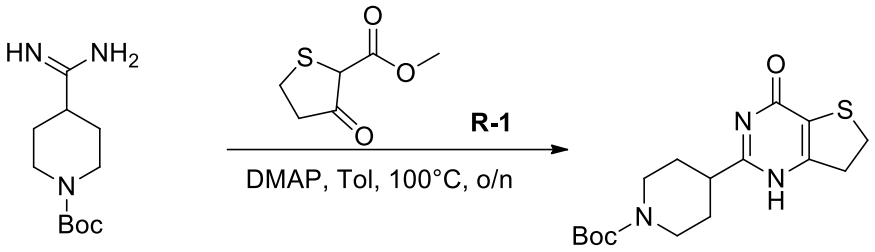


02284-0 **02284-1**

To a solution of N-Boc-4-piperidinylcarboxamide (4.6 g, 20.15 mmol) in DCM (10 mL) was added triethyl oxonium tetrafluoroborate (3.83 g, 20.15 mmol) at room temperature, The mixture was stirred at room temperature for 2 hours. Then, ammonia in methanol solution (32 mL, 7 mol/L) was added dropwise to the reaction mixture and stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure to afford an off-white solid crude product (5.56 g, 100% yield), which was used directly in the next step.

ESI-MS m/z calcd for $[C_{11}H_{21}N_3O_2]$ $[M+H]^+$: 228.2; found: 228.0

2.2 4-(4-Oxo-1,4,6,7-tetrahydrothieno[3,2-d]pyrimidin-2-yl)piperidine-1-carboxylic acid tert-butyl ester(02284-2)



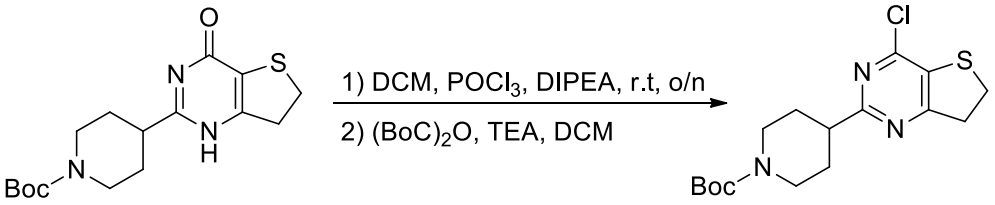
02284-1 **02284-2**

To a solution of 4-aminocarbonylpiperidine-1-carboxylic acid tert-butyl ester (5.56 g, 20.15 mmol) in toluene (30 mL) was added methyl 3-oxotetrahydrothiophen-2-carboxylate (1.6 g, 10.0 mmol) and DMAP (739 mg, 6.05 mmol). The mixture was stirred overnight at 100 °C. Upon complete consumption of the starting material, the mixture was concentrated under reduced pressure. Water (50 mL) was added, and the crude product was extracted three times with DCM (50 mL). The combined organic layers were washed with saturated saline solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/DCM = 0/1–1/0, silica gel-CS 40 g, 40 mL/min, silica gel, UV 254), yielding a white solid product (820 mg, 24.33% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{23}N_3O_3S]$ $[M+H]^+$: 338.1; found: 338.0

2.3

4-(4-Chloro-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)piperidine-1-carboxylic acid tert-butyl ester(02284-3)



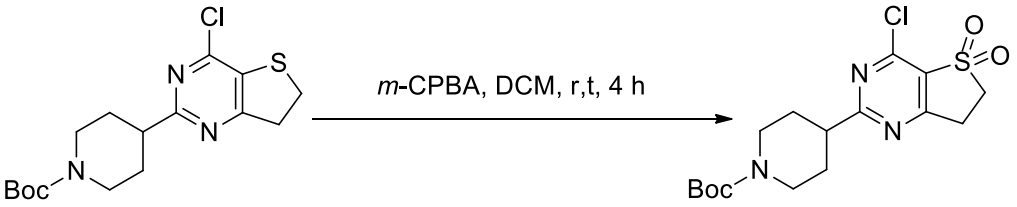
02284-2 **02284-3**

To a solution of 4-(4-oxo-1,4,6,7-tetrahydrothieno[3,2-d]pyrimidin-2-yl)piperidine-1-carboxylic acid tert-butyl ester (145 mg, 0.43 mmol) in DCM (10 mL) was added $POCl_3$ (198 mg, 1.29 mmol) and DIEA (56 mg, 0.43 mmol). The mixture was stirred overnight at room temperature. Upon complete consumption of the starting material, water (1 mL) was added to the mixture and stirred for 30 minutes at room temperature. TEA (1 mL) and $(Boc)_2O$ (141 mg, 0.645 mmol) were then added to the mixture, which was stirred at room temperature for a further 2 hours. The mixture was concentrated under reduced pressure, to which water (10 mL) was added, followed by extraction three times with DCM (10 mL). The combined organic layers were washed with saturated saline solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography

(EA/PE = 0/1–1/1, silica gel-CS 20 g, 30 mL/min, silica gel, UV 254), yielding a yellow solid product (130 mg, 85.1% yield).

ESI-MS m/z calcd for $[C_{16}H_{22}ClN_3O_2S]$ $[M-56+H]^+$: 300.1; found: 300.0

2.44-(4-Chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)piperidine-1-carboxylic acid tert-butyl ester(02284-4)



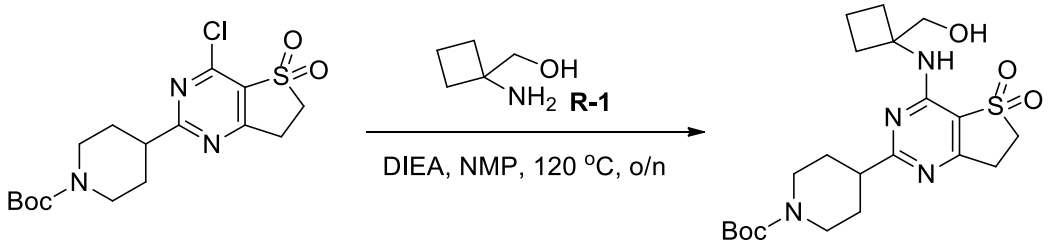
02284-3 **02284-4**

To a solution of 4-(4-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)piperidine-1-carboxylic acid tert-butyl ester (130 mg, 0.365 mmol) in DCM (10 mL) was added m-CPBA (85%, 371.7 mg, 2.15 mmol).The mixture was stirred at room temperature for 4 hours. Upon complete consumption of the starting material, the mixture was concentrated under reduced pressure. Saturated $NaHCO_3$ solution (10 mL) was added, followed by extraction with DCM (10 mL) three times. The combined organic layers were washed with saturated saline solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1–1/0, silica gel-CS 20 g, 30 mL/min, silica gel, UV 254), yielding a yellow solid product (101 mg, 71.4% yield).

ESI-MS m/z calcd for $[C_{16}H_{22}ClN_3O_4S]$ $[M-56+H]^+$: 332.1; found: 332.0

2.5

4-(4-((1-(Hydroxymethyl)cyclobutyl)amino)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)piperidine-1-carboxylic acid tert-butyl ester(MX02284-5)



02284-4 **02284-5**

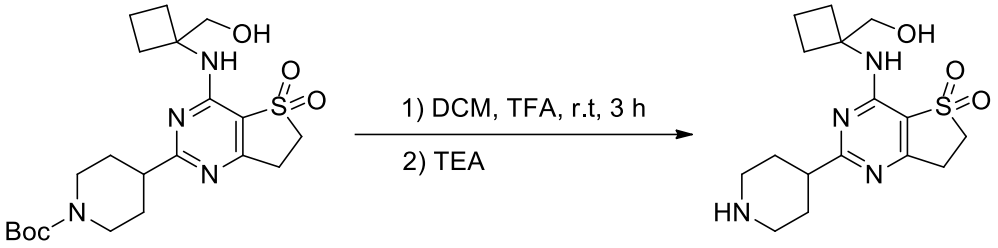
To a solution of tert-butyl 4-(4-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)piperidine-1-carboxylate (90 mg, 0.232 mmol) was dissolved in NMP (3 mL) was added 1-aminocyclobutanemethanol (23.5 mg, 0.232 mmol) and DIE (90 mg, 0.232 mmol), to which 1-aminocyclobutanemethanol (23.5 mg, 0.232 mmol) and DIEA (1 mL) were added. The

mixture was stirred overnight at 120°C. Upon complete consumption of the starting material, the mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19 × 250 mm, 20 mL/min, UV 254] to yield a brown solid product (92 mg, 88% purity, 76.8% yield).

ESI-MS m/z calcd for $[C_{21}H_{32}N_4O_5S]$ $[M+H]^+$: 453.2; found: 453.2

2.6

4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(piperidin-4-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5,5-dioxide(02284-6)



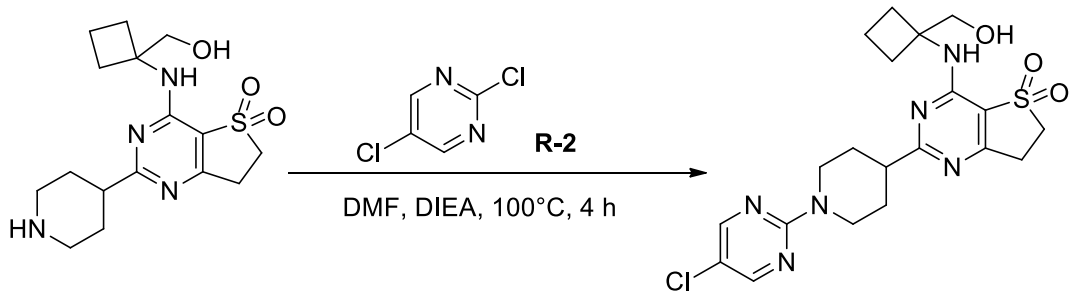
02284-5 **02284-6**

To a solution of 4-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)piperidine-1-carboxylic acid tert-butyl ester (92 mg, 88% purity, 0.179 mmol) in DCM (80 mL) was added TFA (0.4 mL). The reaction mixture was stirred at room temperature under nitrogen for 3 hours. Upon depletion of the starting material, the reaction solution was neutralised to pH 7 with TEA and concentrated under reduced pressure to afford a brown oily product (63.1 mg, 100% yield), which was directly used in the subsequent reaction.

ESI-MS m/z calcd for $[C_{16}H_{24}N_4O_3S]$ $[M-56+H]^+$: 353.2; found: 353.2

2.7

2-(1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)-4-((1-hydroxymethylcyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5,5-dioxide(MX02284)



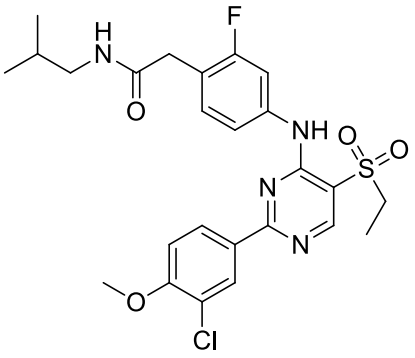
02284-6 **MX02284**

To a solution of 4-((1-(hydroxymethyl)cyclobutyl)amino)-2-(piperidin-4-yl)-6,7-

dihydrothieno[3,2-d]pyrimidine 5,5-dioxide (63.1 mg, 0.179 mmol) in DMF (5 mL), 2, 5-dichloropyridine (39.3 mg, 0.264 mmol) and DIEA (1 mL) were added to a solution of 4-((1-(hydroxymethyl)cyclobutyl)amino)-2-(piperidin-4-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5,5-dioxide (63.1 mg, 0.179 mmol) in DMF (5 mL). The mixture was stirred under nitrogen at 100°C for 4 hours. Upon complete consumption of the starting materials, the reaction mixture was concentrated under vacuum. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19 × 250 mm, 20 mL/min, UV 254] to yield a pale yellow solid (50 mg, 75.7% yield).

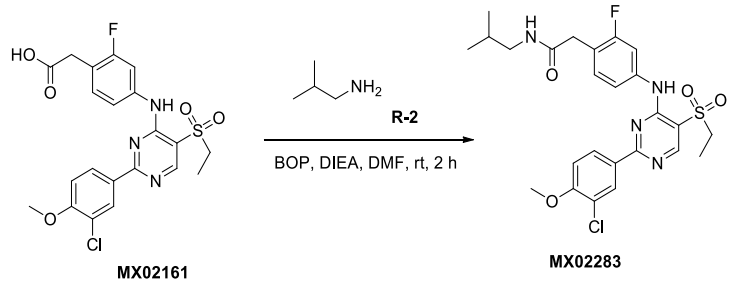
ESI-MS m/z calcd for [$C_{20}H_{25}ClN_6O_3S$] $[M-56+H]^+$: 465.1; found: 465.0

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.42 (s, 2H), 6.69 (s, 1H), 5.02 (t, J = 5.2 Hz, 1H), 4.63 (d, J = 12.8 Hz, 2H), 3.66 (d, J = 5.6 Hz, 2H), 3.58 (t, J = 6.8 Hz, 2H), 3.21 (t, J = 7.2 Hz, 2H), 3.10 – 3.07 (m, 2H), 3.00 – 2.93 (m, 1H), 2.47 – 2.39 (m, 2H), 2.12 – 2.05 (m, 2H), 1.99 – 1.96 (m, 2H), 1.76 – 1.60 (m, 4H).



MX02283

1. Synthetic scheme:

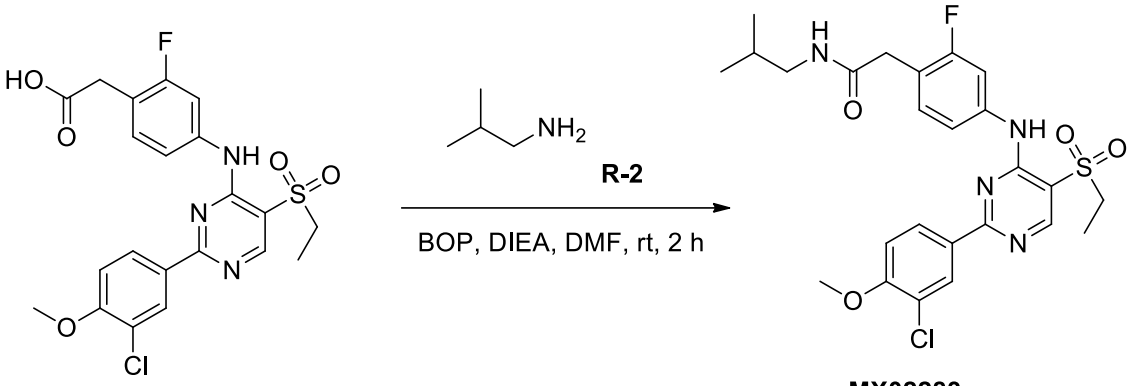


MX02161 **MX02283**

2. Experimental section:

2.1

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)isobutylacetamide(MX02283)

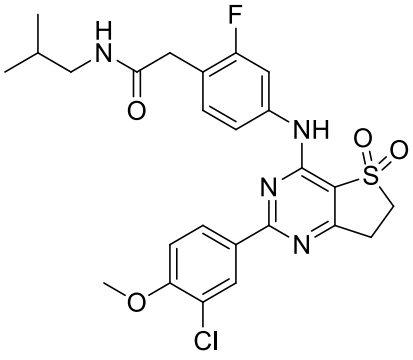


MX02161 **MX02283**

To a solution of 2-(4-((2-(3-chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (50 mg, 0.104 mmol) in DMF (3 mL), isobutylamine (9.2 mg, 0.125 mmol), DIPEA (23 mg, 0.18 mmol), and BOP (40 mg, 0.09 mmol) were added at room temperature. The mixture was stirred at room temperature for 2 hours until the starting material was consumed. The reaction mixture was concentrated under vacuum, and the crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (30 mg, 53.8% yield).

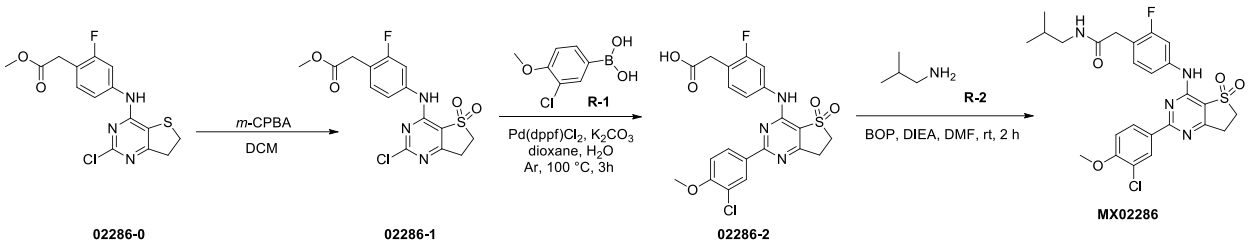
ESI-MS *m/z* calcd for $[C_{25}H_{28}ClFN_4O_4S]$ $[M+H]^+$: 535.2; found: 534.7

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.78 (s, 1H), 8.29 – 8.25 (m, 2H), 8.06 – 8.05 (m, 1H), 7.68 (d, J = 11.2 Hz, 1H), 7.38 – 7.33 (m, 3H), 3.96 (s, 3H), 3.56 – 3.51 (m, 4H), 2.91 (t, J = 6.4 Hz, 2H), 1.74 – 1.67 (m, 1H), 1.27 – 1.22 (m, 3H), 0.85 (d, J = 6.8 Hz, 6H).



MX02286

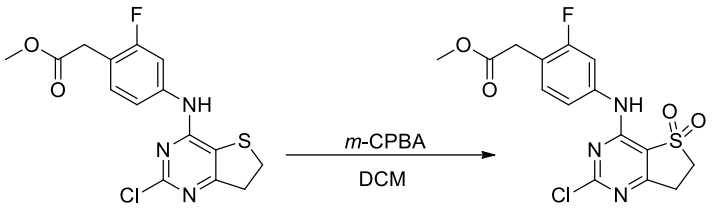
1. Synthetic scheme:



2. Experimental section:

2.1

Methyl-2-(4-(((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02286-1)

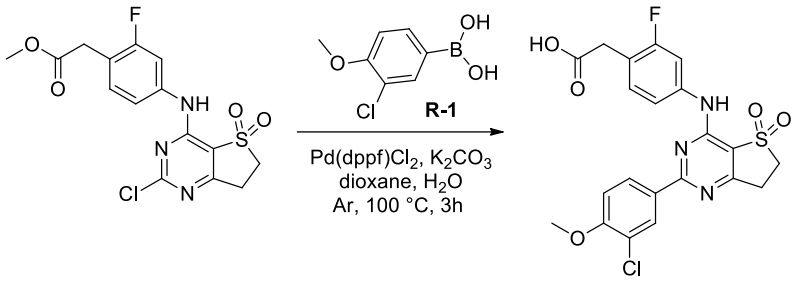


To a solution of 2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (200 mg, 0.57 mmol) in dichloromethane (DCM, 10 mL), m-CPBA (85%, 216.4 mg, 1.25 mmol) was added at room temperature,. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and the crude product was treated with saturated aqueous $NaHCO_3$ solution (40 mL). The mixture was extracted with ethyl acetate (EA, 40 mL) twice, and the combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (DCM/MeOH = 1:0 to 20:1, silica gel, 20 g, 25 mL/min, UV 254) to afford a yellow solid product (128 mg, 58.7% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{13}ClFN_3O_4S]$ $[M+H]^+$: 386.0; found: 385.7

2.2

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(02286-2)



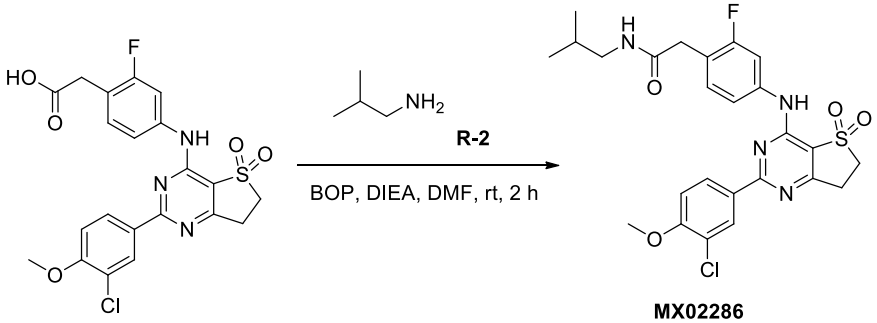
02286-1 02286-2

To a solution of 2-(4-((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (70 mg, 0.18 mmol) and (3-chloro-4-methoxyphenyl)boronic acid (33.8 mg, 0.18 mmol) in 1,4-dioxane/water (4 mL, v/v 3:1), $Pd(dppf)Cl_2$ (14.2 mg, 0.0193 mmol) and K_2CO_3 (74.6 mg, 0.54 mmol) were added at 100°C under a nitrogen atmosphere. The mixture was stirred at 100°C under nitrogen for 3 hours. Then, water (20 mL) was added, and the mixture was extracted with ethyl acetate (EA, 20 mL) twice. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (9.16 mg, 9.68% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{17}ClFN_3O_5S]$ $[M+H]^+$: 478.1; found: 477.6

2.3

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutylethanamide(MX02286)



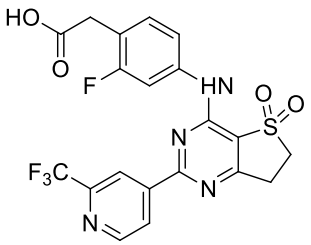
02286-2 MX02286

At room temperature, to a solution of 2-(4-((2-(3-chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (30 mg, 0.06 mmol) in DMF (2 mL), isobutylamine (5 mg, 0.07 mmol), DIPEA (23 mg, 0.18 mmol), and BOP (40 mg, 0.09 mmol) were added. The mixture was stirred at room temperature for 2 hours until the starting material was consumed. The reaction mixture was concentrated under vacuum, and the crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-

Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (15 mg, 45% yield).

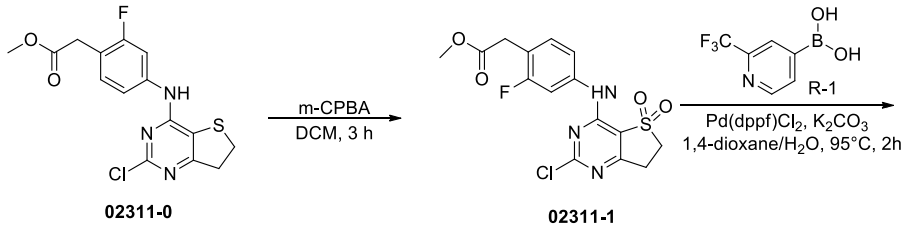
ESI-MS *m/z* calcd for $[C_{25}H_{26}ClFN_4O_4S]$ $[M+H]^+$: 533.1; found: 532.6

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 8.22 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.10 (t, *J* = 6.0 Hz, 1H), 7.59 (dd, *J* = 12.0, 2.0 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.35 – 7.30 (m, 2H), 3.94 (s, 3H), 3.71 (t, *J* = 6.8 Hz, 2H), 3.50 (s, 2H), 3.40 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 6.0 Hz, 2H), 1.74 – 1.67 (m, 1H), 0.85 (d, *J* = 6.4 Hz, 6H).



MX02311

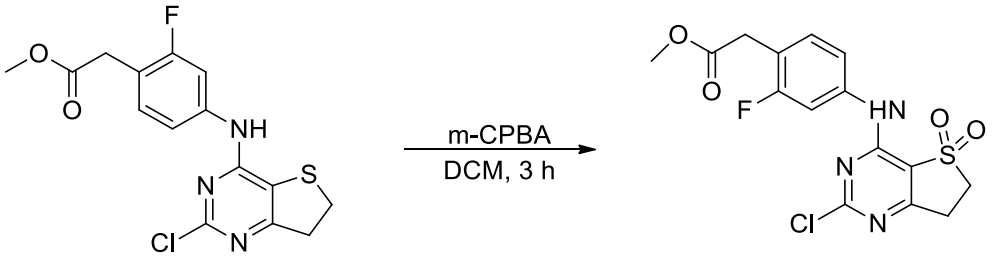
1. Synthetic scheme:



2. Experimental section:

2.1

Methyl-2-(4-(((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl) amino)-2-fluorophenyl)acetate(02311-1)



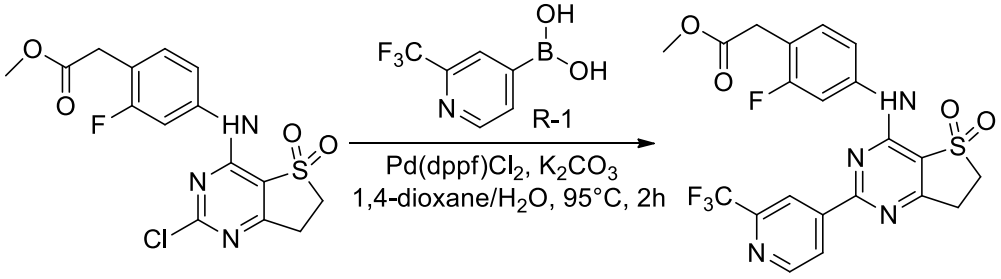
02311-0 02311-1

To a solution of 2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (200.0 mg, 0.57 mmol) in DCM (10 mL)was added *m*-CPBA (85%, 216.4 mg, 1.25 mmol) at room temperature. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. Saturated aqueous $NaHCO_3$ solution (40 mL) was added, and the mixture was extracted with ethyl acetate (EA, 40 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (DCM/MeOH = 1:0 to 20:1, silica gel, 20 g, 25 mL/min, UV 254) to afford a yellow solid product (128 mg, 58.7% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{13}ClFN_3O_4S]$ $[M+H]^+$: 386.0; found: 385.7

2.2

Methyl-2-(4-((5,5-dioxo-2-(2-(trifluoromethyl)pyridin-4-yl)-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02311-2)



02311-1 02311-2

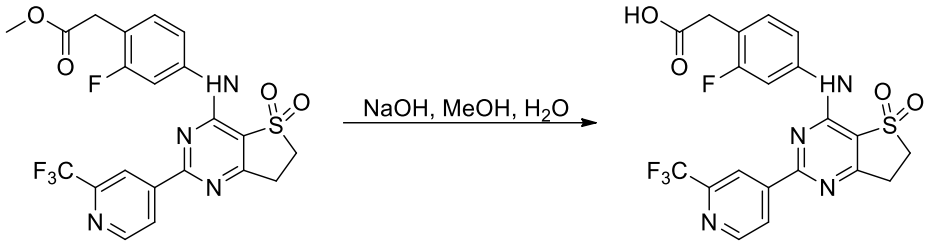
To a solution of 2-(4-(2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (70 mg, 0.181 mmol) in 1,4-dioxane/water (5 mL, v/v 4:1), (2-(trifluoromethyl)pyridin-4-yl)boronic acid (50.2 mg, 0.272 mmol), K_2CO_3 (100.3 mg, 0.726 mmol), and $Pd(dppf)Cl_2$ (14.8 mg, 0.018 mmol) were added at room temperature. The mixture was heated to 95°C and stirred under nitrogen for 2 hours. After cooling, water (10 mL) was added, and the mixture was extracted with ethyl acetate (EA, 20 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was

purified by column chromatography (DCM/MeOH = 0~1%, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a yellow solid product (41 mg, 45.5% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{16}F_4N_4O_4S]$ $[M+H]^+$:497.1; found: 496.9

2.3

2-(4-((5,5-Dioxo-2-(2-(trifluoromethyl)pyridin-4-yl)-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02311)

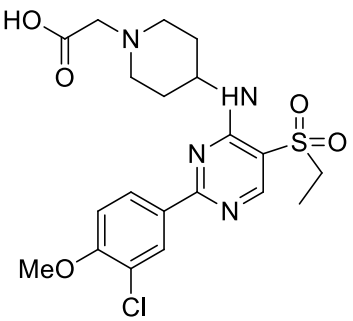


02311-2 MX02311

To a solution of 2-(4-(((5,5-dioxo-2-(2-(trifluoromethyl)pyridin-4-yl)-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (41 mg, 0.083 mmol) in methanol (3 mL), NaOH (19.8 mg, 0.496 mmol) in water (1 mL) was added at room temperature. The mixture was stirred at room temperature for 2 hours. The pH of the solution was adjusted to 6 with acetic acid. The mixture was filtered and purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (25.46 mg, 63.6% yield).

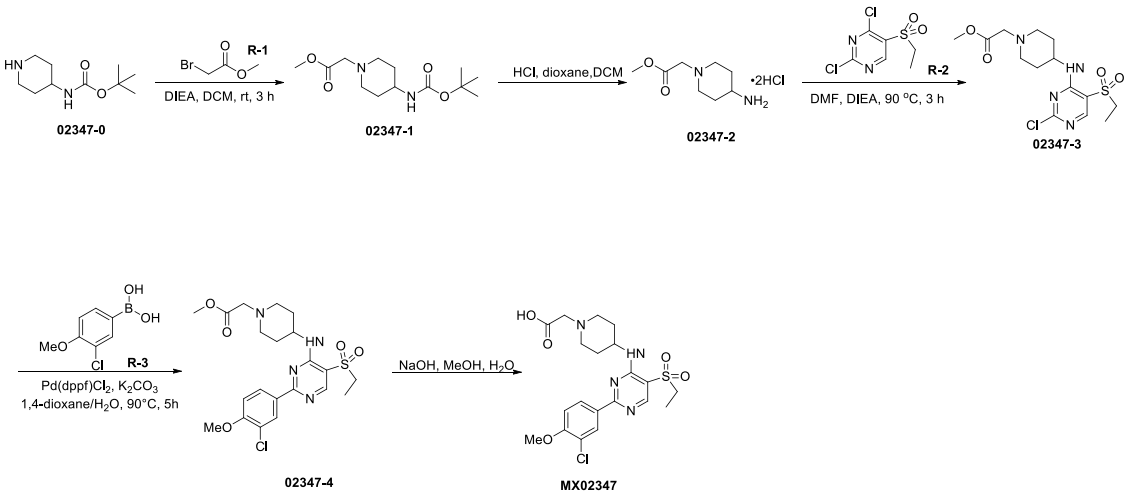
ESI-MS *m/z* calcd for $[C_{20}H_{14}F_4N_4O_4S]$ $[M+H]^+$:483.1; found: 483.3

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.87 (d, J = 5.2 Hz, 1H), 8.66 (s, 1H), 8.48 – 8.46 (m, 1H), 7.55 – 7.52 (m, 1H), 7.41 – 7.36 (m, 2H), 3.71 (t, J = 7.2 Hz, 2H), 3.56 (s, 2H), 3.52 – 3.49 (m, 2H).



MX02347

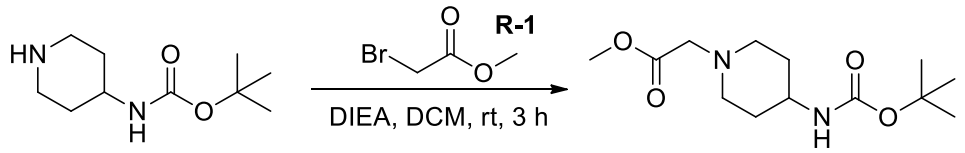
1. Synthetic scheme:



2. Experimental section:

2.1

Methyl 2-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)acetate(02347-1)



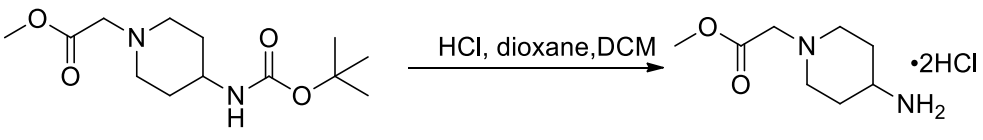
02347-0 **02347-1**

tert-Butyl piperidine-4-carbamate (2 g, 9.99 mmol), ethyl bromoacetate (1.83 g, 11.98 mmol) and DIPEA (1.94 g, 14.98 mmol) were stirred in DCM (25 mL) at room temperature for 3 hours. After cooling, the reaction mixture was poured into ice-water (20 mL) and extracted three times with DCM (20 mL). The combined organic layers were washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. A yellow solid product was obtained (1.61 g, 59% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{24}N_2O_4]$ $[M+H]^+$: 272.2; found: 272.0

2.2

Methyl 2-(4-aminopiperidin-1-yl)acetate dihydrochloride(02347-2)



02347-1 **02347-2**

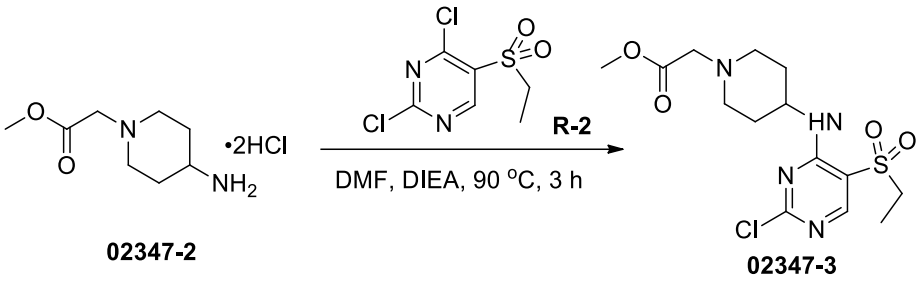
To a solution of 2-(4-((tert-butyl carbamate)amino)piperidin-1-yl)acetic acid methyl ester (1.61 g, 5.91 mmol) in DCM (30 mL), 4N hydrochloric acid in dioxane solution (10 mL) was added at 0 °C. The reaction mixture was slowly brought to room temperature and stirred for 4 hours until the starting material was consumed. The mixture was concentrated under reduced

pressure. The crude product was washed with MTBE (15 mL) to afford a white solid product (1.44 g, 100% yield).

ESI-MS *m/z* calcd for $[C_8H_{16}N_2O_2]$ $[M+H]^+$: 173.1.1; found: 173.1

2.3

Methyl 2-(4-(((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)piperidin-1-yl)acetate(02347-3)

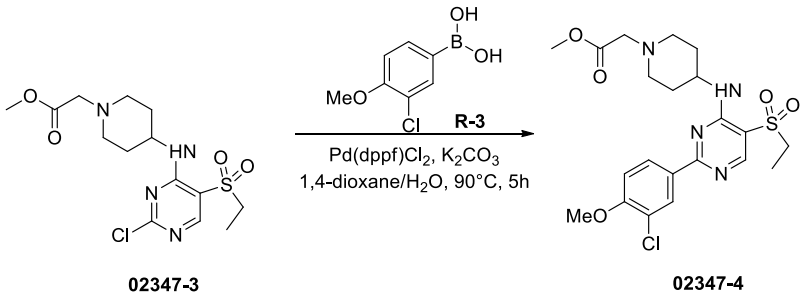


To a solution of 2,4-dichloro-5-(ethylsulfonyl)pyrimidine (80 mg, 0.33 mmol) in DMF (3 mL), 2-(4-aminopiperidin-1-yl)acetic acid methyl ester dihydrochloride (81 mg, 0.33 mmol) and DIPEA (173 mg, 1.34 mmol) were added. The mixture was stirred at 90 °C under nitrogen for 3 hours until the starting material was consumed. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (EA, 20 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0:1 to 1:1, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a yellow solid product (67 mg, 63% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{21}ClN_4O_4S]$ $[M+H]^+$: 377.1; found: 377.2

2.4

Methyl 2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)piperidin-1-yl)acetate(02347-4)



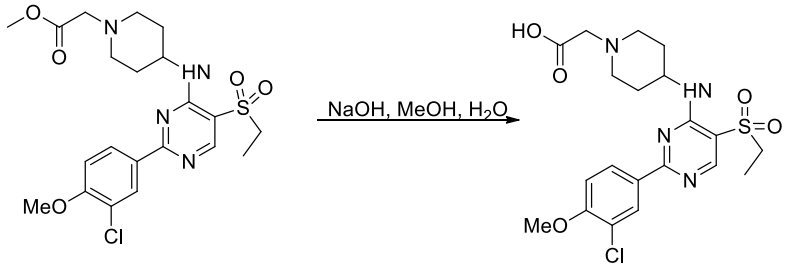
To a solution of 2-(4-(((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)piperidin-1-yl)acetic acid methyl ester (67 mg, 0.18 mmol) in 1,4-dioxane/water (2.5 mL, v/v 5:1), (3-chloro-4-methoxyphenyl)boronic acid (39 mg, 0.21 mmol), K_2CO_3 (50 mg, 0.36 mmol), and

$Pd(dppf)Cl_2$ (13 mg, 0.018 mmol) were added at 90 °C under nitrogen. The mixture was stirred at 90 °C under nitrogen for 5 hours until the starting material was consumed. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (EA, 20 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0:1 to 1:1, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a yellow solid product (27 mg, 32% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{27}ClN_4O_5S]$ $[M+H]^+$: 483.1; found: 483.2

2.5

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)piperidin-1-yl)acetic acid(MX02347)

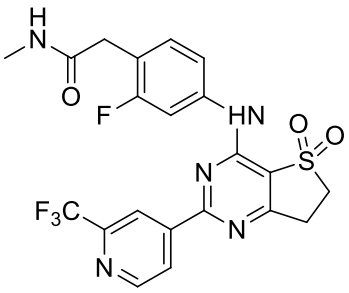


02347-4 MX02347

To a solution of 2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)piperidin-1-yl)acetic acid methyl ester in MeOH/THF (2 mL, v/v 1:1), 2N NaOH aqueous solution was added at room temperature to adjust the pH to 12. The mixture was stirred at room temperature under nitrogen for 3 hours until the starting material was consumed. The pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated, and the crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (12 mg, 46% yield).

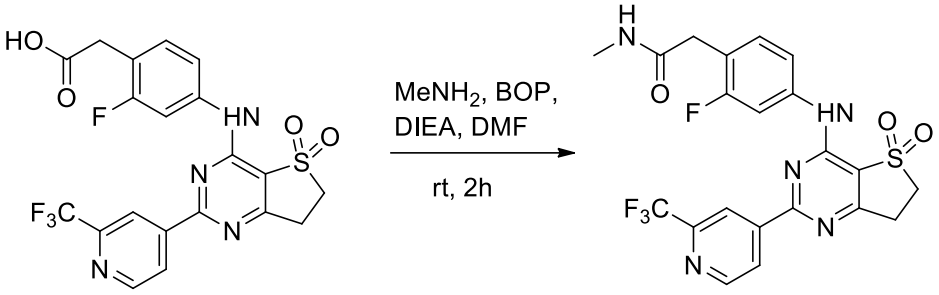
ESI-MS *m/z* calcd for $[C_{20}H_{25}ClN_4O_5S]$ $[M+H]^+$: 469.1; found: 469.2

^1H NMR (400 MHz, Methanol-d_4) δ 8.84 – 8.78 (m, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 4.29 – 4.19 (m, 1H), 3.96 (s, 3H), 3.63 – 3.59 (m, 4H), 3.27 – 3.17 (m, 2H), 2.78 (q, J = 7.2 Hz, 2H), 2.33 – 2.20 (m, 2H), 2.03 – 1.94 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H).



MX02358

1. Synthetic scheme:

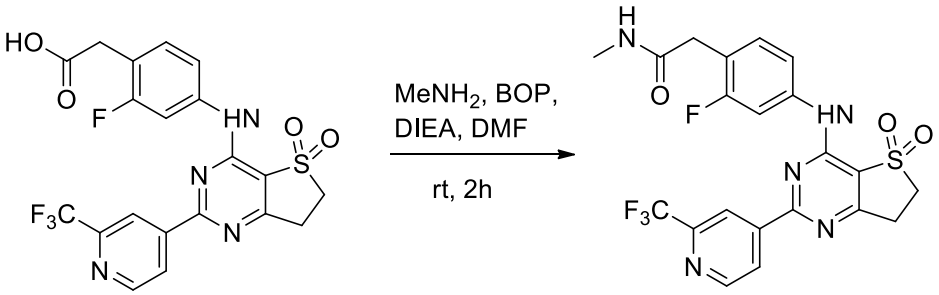


MX02311 **MX02358**

2. Experimental section:

2.1

2-(4-((5,5-Dioxo-2-(2-(trifluoromethyl)pyridin-4-yl)-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-methylacetamide(MX02358)



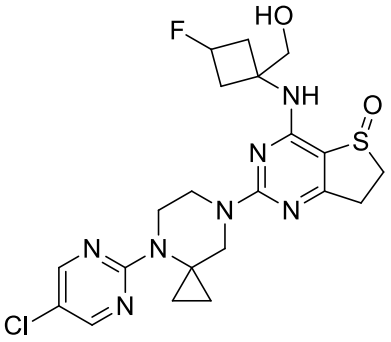
MX02311 **MX02358**

To a solution of 2-(4-((5,5-dioxo-2-(2-(trifluoromethyl)pyridin-4-yl)-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (17 mg, 0.035 mmol), BOP (23.4 mg, 0.053 mmol), and DIEA (13.6 mg, 0.105 mmol) in DMF (2 mL), 2 M methylamine in THF (0.05 mL, 0.105 mmol) was added at room temperature. The mixture was stirred at room temperature for 2 hours, and then the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L

NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (10.8 mg, 62.3% yield).

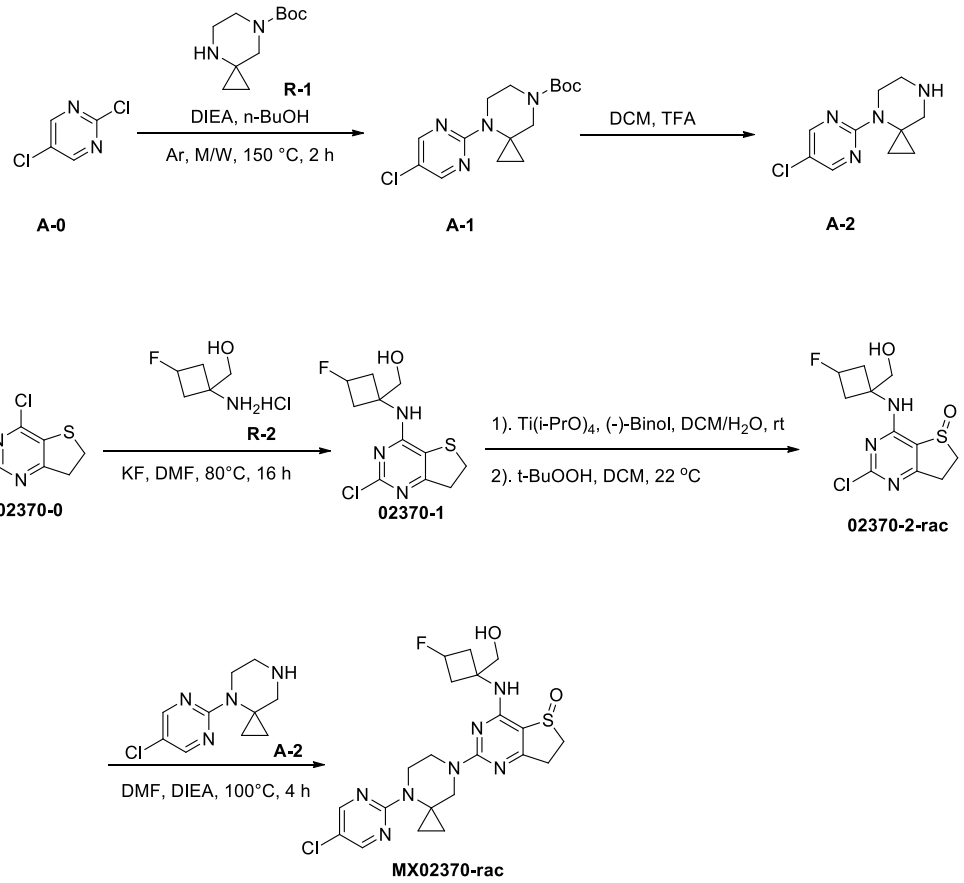
ESI-MS *m/z* calcd for $[C_{21}H_{17}F_4N_5O_3S]$ $[M+H]^+$: 496.1; found: 495.9

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.87 (d, J = 5.2 Hz, 1H), 8.64 (s, 1H), 8.48 (d, J = 5.2 Hz, 1H), 7.62 (dd, J = 11.6, 2.0 Hz, 1H), 7.45 (dd, J = 8.4, 2.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 3.71 (t, J = 6.8 Hz, 2H), 3.60 (s, 2H), 3.51 (t, J = 7.2 Hz, 2H), 2.76 (s, 3H).



MX02370-rac

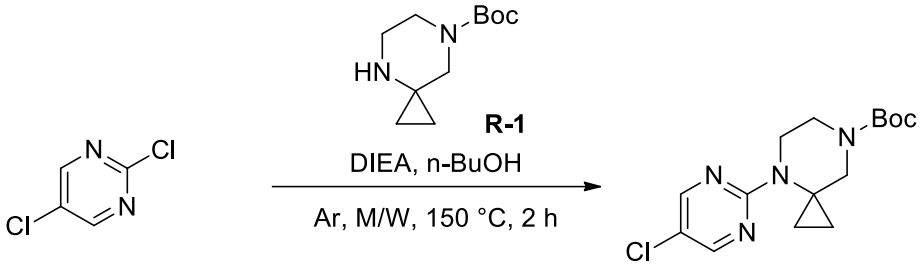
1. Synthetic scheme:



2. Experimental section:

2.1

4-(5-Chloropyrimidin-2-yl)-4,7-diazaspiro[2.5]octane-7-carboxylic acid tert-butyl ester(A-1)



A-0 **A-1**

A mixture of 2,5-dichloropyrimidine (200 mg, 1.34 mmol), 4,7-diazaspiro[2.5]octane-7-carboxylic acid tert-butyl ester (711 mg, 3.35 mmol), and DIPEA (1.1 mL, 6.7 mmol) in *n*-butanol (10 mL), the mixture was stirred at 150 °C under argon atmosphere under microwave conditions for 2 hours. After cooling, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0:1 to 1:9, silica gel CS 40 g, 40 mL/min, silica gel, UV 254) to afford a colorless oily product (71 mg, 16.3% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{21}ClN_4O_2]$ $[M-56+H]^+$: 269.1; found: 268.9

2.2

4-(5-Chloropyrimidin-2-yl)-4,7-diazaspiro[2.5]octane(A-2)



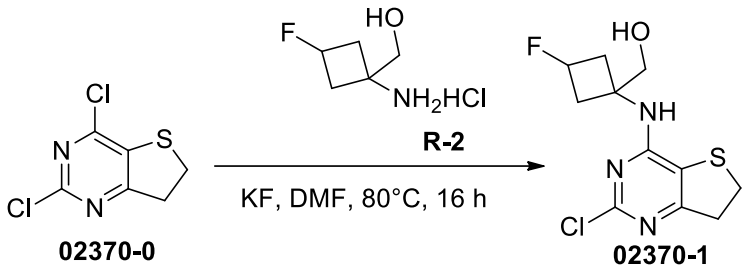
A-1 **A-2**

To a solution of 4-(5-chloropyrimidin-2-yl)-4,7-diazaspiro[2.5]octane-7-carboxylic acid tert-butyl ester (71 mg, 0.22 mmol) in DCM (3 mL), TFA (0.3 mL) was added at room temperature. The reaction mixture was stirred at room temperature under nitrogen for 3 hours until the starting material was consumed. The mixture was concentrated under reduced pressure to dryness, affording a white solid product (134.7 mg, 55% purity, 100% yield).

ESI-MS *m/z* calcd for $[C_{10}H_{13}ClN_4]$ $[M+H]^+$: 225.1; found: 225.4

2.3

(1-((2-Chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-3-fluoro-cyclobutyl)methanol(02370-1)

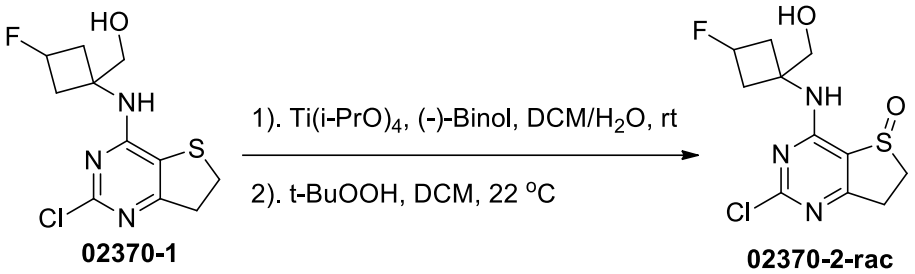


To a solution of 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidine (113 mg, 0.545 mmol) in DMF (4 mL), (3-fluoro-1-aminocyclobutyl)methanol hydrochloride (70.7 mg, 0.454 mmol) and KF (79.1 mg, 1.362 mmol) were added at 80°C. The mixture was stirred at 80°C for 16 hours. The solvent was removed under reduced pressure. Water (10 mL) was added, and the mixture was extracted with DCM (10 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0:1 to 100%, silica gel CS 20 g, 30 mL/min, silica gel, UV 254) to afford a yellow solid product (100 mg, 75.9% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{13}ClFN_3OS]$ $[M+H]^+$: 290.1; found: 289.9

2.4

2-Chloro-4-((3-fluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(02370-2-rac)

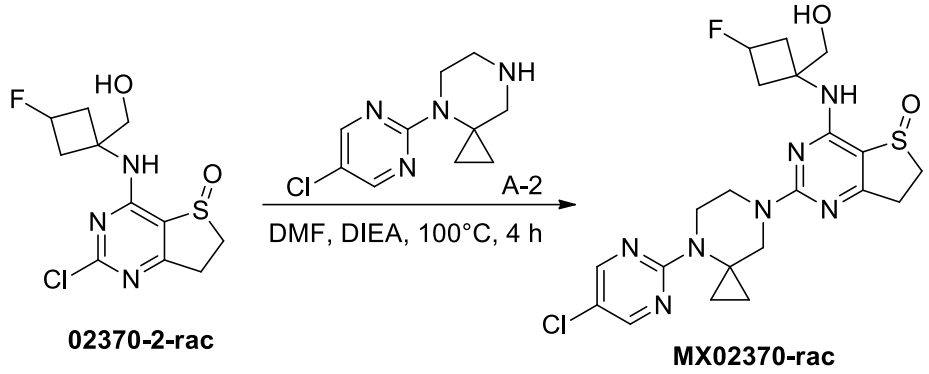


To a solution of 1-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-3-fluorocyclobutyl)methanol (100 mg, 0.345 mmol) and S-1,1'-binaphthol (9.8 mg, 0.0345 mmol) in DCM (10 mL), titanium tetraisopropoxide (9.8 mg, 0.0345 mmol) and water (12.4 mg, 0.69 mmol) were added at room temperature. The mixture was stirred at room temperature for 1 hour. 70% tert-butyl hydroperoxide aqueous solution (88.7 mg, 0.69 mmol) was added all at once. Then the mixture was stirred at room temperature for 2 hours. Water (10 mL) was added, and the mixture was extracted with DCM (10 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (DCM/MeOH = 1:0 to 10:1, silica gel CS 20 g, 30 mL/min, silica gel, UV 254) to afford a yellow solid product (85.0 mg, 80.6% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{13}ClFN_3O_2S]$ $[M+H]^+$: 306.0; found: 305.8

2.5

2-(4,5-Dihydro-2H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-4-((1-(hydroxymethyl)-3-fluoro-cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02370-rac)

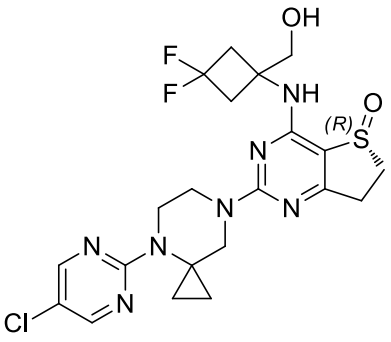


02370-2-rac **MX02370-rac**

To a solution of 2-chloro-4-((1-(hydroxymethyl)-3-fluorocyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (40 mg, 0.13 mmol) in DMF (4 mL), 4-(5-chloropyrimidin-2-yl)-4,7-diazaspiro[2.5]octane (63.9 mg, 55% purity, 0.157 mmol) and DIEA (0.5 mL) were added at room temperature. The mixture was stirred at 100°C for 4 hours. The solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (33 mg, 51.1% yield).

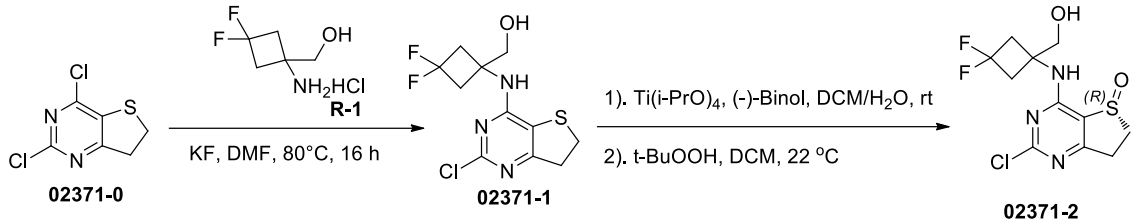
ESI-MS *m/z* calcd for $[C_{21}H_{25}ClFN_7O_2S]$ $[M+H]^+$: 494.2; found: 494..2

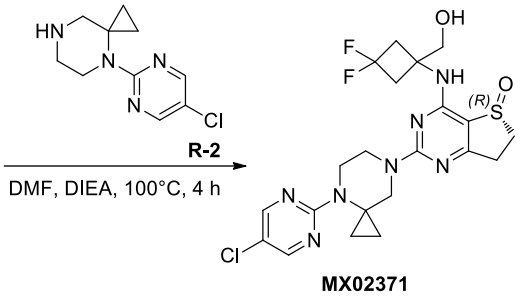
^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 2H), 7.89 – 7.60 (m, 1H), 5.16 – 4.86 (m, 2H), 3.94 – 3.41 (m, 9H), 3.25 – 3.13 (m, 1H), 2.96 – 2.64 (m, 4H), 2.49 – 2.08 (m, 2H), 0.96(s, 4H).



MX02371

1. Synthetic scheme:

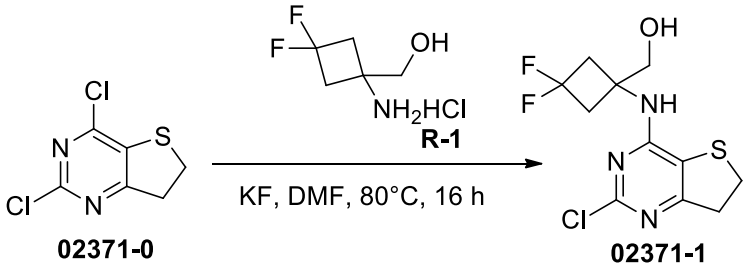




2. Experimental section:

2.1

(1-((2-Chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-3,3-difluoro-cyclobutyl)methanol(02371-1)

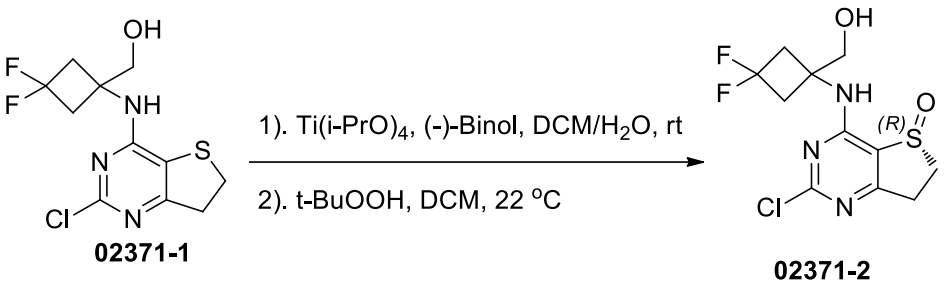


To a solution of 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidine (270 mg, 1.304 mmol) in DMF (5 mL), (1-amino-3,3-difluorocyclobutyl)methanol hydrochloride (181.1 mg, 1.043 mmol) and KF (181.5 mg, 3.13 mmol) were added at 80°C. The mixture was stirred at 80°C for 16 hours. The solvent was removed under reduced pressure. Water (20 mL) was added, and the mixture was extracted with DCM (20 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0:1 to 100%, silica gel CS 20 g, 30 mL/min, silica gel, UV 254) to afford a yellow solid product (170 mg, 52.8% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{12}ClF_2N_3OS]$ $[M+H]^+$: 308.0; found: 308.2

2.2

(R)-2-Chloro-4-((1-(hydroxymethyl)-3,3-difluoro-cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(02371-2)

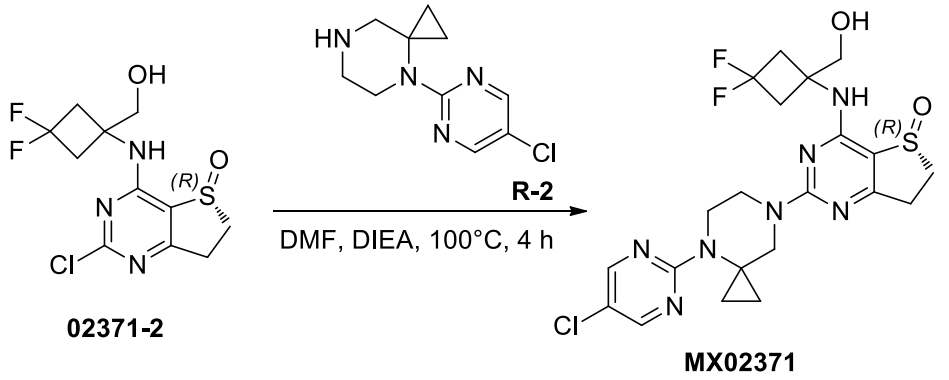


To a solution of (1-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-3,3-difluorocyclobutyl)methanol (100 mg, 0.325 mmol) and S-1,1'-binaphthol (9.2 mg, 0.0325 mmol) in DCM (10 mL), titanium tetraisopropoxide (9.2 mg, 0.0325 mmol) and water (11.7 mg, 0.65 mmol) were added at room temperature. The mixture was stirred at room temperature for 1 hour. 70% tert-butyl hydroperoxide aqueous solution (88.7 mg, 0.69 mmol) was added all at once. Then the mixture was stirred at room temperature for 2 hours. Water (10 mL) was added, and the mixture was extracted with DCM (10 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (DCM/MeOH = 1:0 to 10:1, silica gel CS 20 g, 30 mL/min, silica gel, UV 254) to afford a yellow solid product (80.0 mg, 76.0% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{12}ClF_2N_3O_2S]$ $[M+H]^+$: 324.0; found: 324.2

2.3

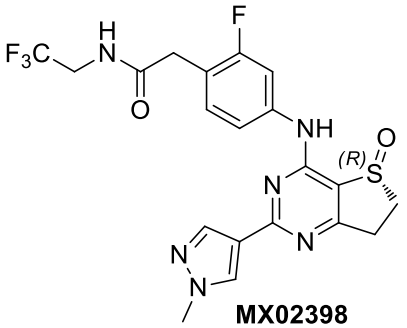
(R)-2-(4,5-dihydro-2H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-4-((1- (hydroxymethyl)-3,3-difluoro-cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02371)



To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)-3,3-difluorocyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (35 mg, 0.108 mmol) in DMF (4 mL), 4-(5-chloropyrimidin-2-yl)-4,7-diazaspiro[2.5]octane (52.8 mg, 55% purity, 0.13 mmol) and DIEA (0.5 mL) were added at 100°C. The mixture was stirred at 100°C for 4 hours. The solvent was removed under reduced pressure. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (39.0 mg, 70.5% yield).

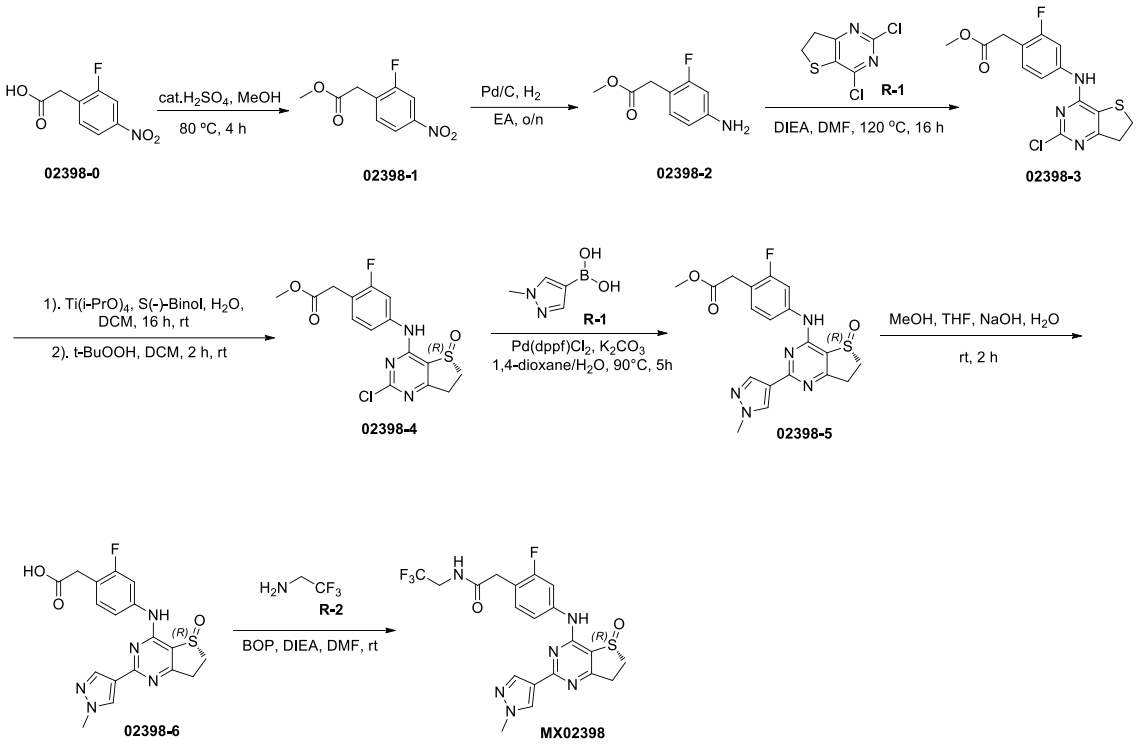
ESI-MS *m/z* calcd for $[C_{21}H_{24}ClF_2N_7O_2S]$ $[M+H]^+$: 512.1; found: 512..2

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 2H), 7.96 – 7.88 (m, 1H), 5.15 (t, J =5.6 Hz, 1H), 3.94 – 3.62 (m, 8H), 3.45 – 3.41 (m, 1H), 3.23 – 3.16 (m, 1H), 2.94 – 2.83 (m, 6H), 0.95(s, 4H).



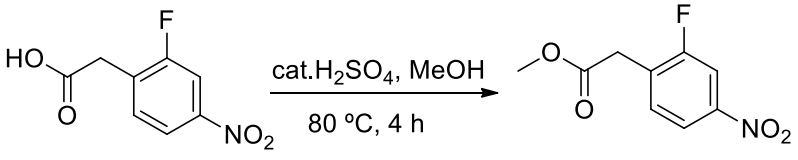
MX02398

1. Synthetic scheme:



2. Experimental section:

2.1 Methyl 2-(2-fluoro-4-nitrophenyl)acetate(02398-1)



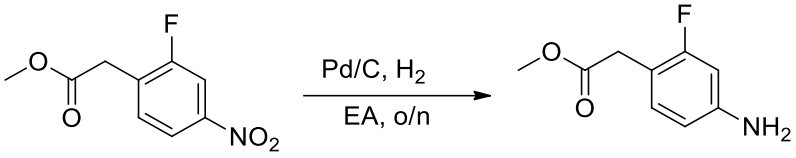
02398-0 **02398-1**

To a solution of 2-(2-fluoro-4-nitrophenyl)acetic acid (4 g, 20.101 mmol) in MeOH (40 mL), concentrated H_2SO_4 (2 mL) was added at room temperature. The mixture was stirred at

80 °C for 4 hours. The reaction mixture was concentrated under reduced pressure. Saturated aqueous $NaHCO_3$ solution (40 mL) was added, and the mixture was extracted with ethyl acetate (EA, 40 mL) twice. The combined organic layers were washed with saturated saturated brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated. A yellow solid product (3.6 g, 84.1% yield) was obtained.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 – 8.08 (m, 2H), 7.70 (t, J = 8.0 Hz, 1H), 3.94 (s, 2H), 3.66 (s, 3H).

2.2 Methyl 2-(4-amino-2-fluorophenyl)acetate(02398-2)



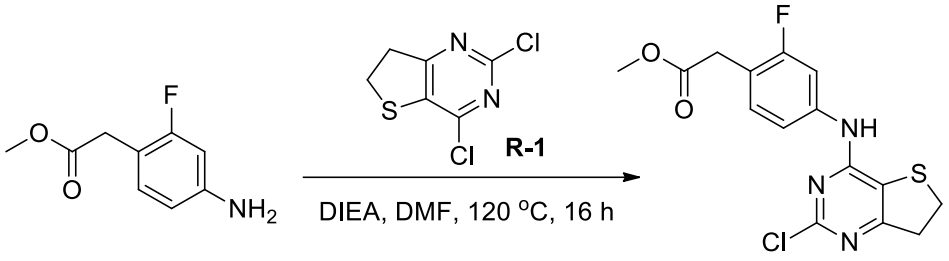
02398-1 **02398-2**

To a solution of 2-(2-fluoro-4-nitrophenyl)acetic acid methyl ester (3.6 g, 16.886 mmol) in ethyl acetate (EA, 40 mL), Pd/C (360 mg) was added at room temperature. The mixture was stirred at room temperature under hydrogen atmosphere overnight. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 4:1, silica gel CS 40 g, 40 mL/min, UV 254) to afford a yellow solid product (2.9 g, 93.9% yield).

ESI-MS *m/z* calcd for $[C_9H_{10}FNO_2]$ $[M+H]^+$: 184.1; found: 184.2

2.3

Methyl-2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02398-3)



02398-2 **02398-3**

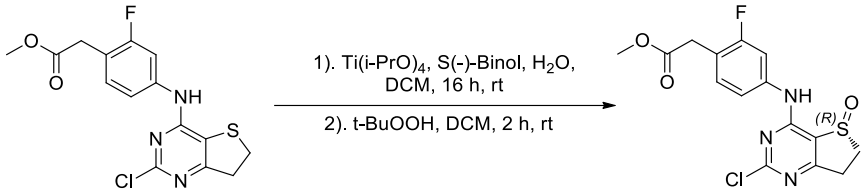
To a solution of 2-(4-amino-2-fluorophenyl)acetic acid methyl ester (3.62 g, 19.76 mmol) and DIPEA (7.65 g, 59.279 mmol) in DMF (40 mL), 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidine (4.09 g, 19.76 mmol) was added at room temperature. The mixture was stirred at 120°C for 16 hours. The reaction mixture was concentrated under reduced pressure. Water (60 mL) was added, and the mixture was extracted with DCM (60 mL) twice. The combined

organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/hexane = 0:1 to 1:0, silica gel CS 40 g, 40 mL/min, UV 254) to afford a yellow solid product (1.58 g, 22.6% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{13}ClFN_3O_2S]$ $[M+H]^+$: 354.0; found: 354.0

2.4

(R)-2-(4-((2-chloro-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester(02398-4)



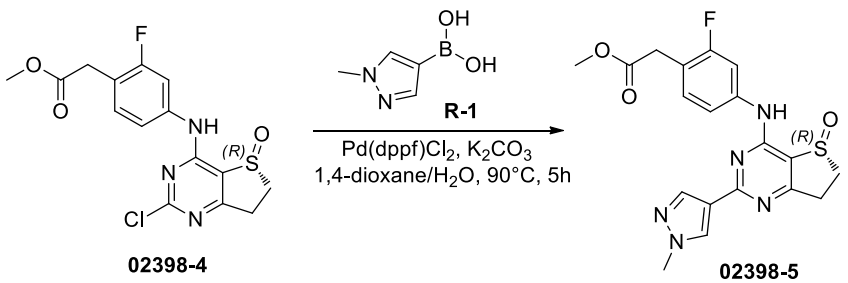
02398-3 02398-4

To a solution of 2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (500 mg, 1.413 mmol) and S-1,1'-binaphthol (40.5 mg, 0.141 mmol) in DCM (10 mL), titanium tetraisopropoxide (20.1 mg, 0.071 mmol) and water (25.4 mg, 1.413 mmol) were added at room temperature. The mixture was stirred under nitrogen atmosphere for 16 hours. Then, 70% tert-butyl hydroperoxide aqueous solution (200 mg, 1.555 mmol) was added all at once. The mixture was stirred at room temperature under nitrogen atmosphere for 2 hours. Water (20 mL) was added, and the mixture was extracted with DCM (60 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (DCM/MeOH = 1:0 to 20:1, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a yellow solid product (392 mg, 75.1% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{13}ClFN_3O_3S]$ $[M+H]^+$: 370.0; found: 369.9

2.5

(R)-2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid methyl ester(02398-5)



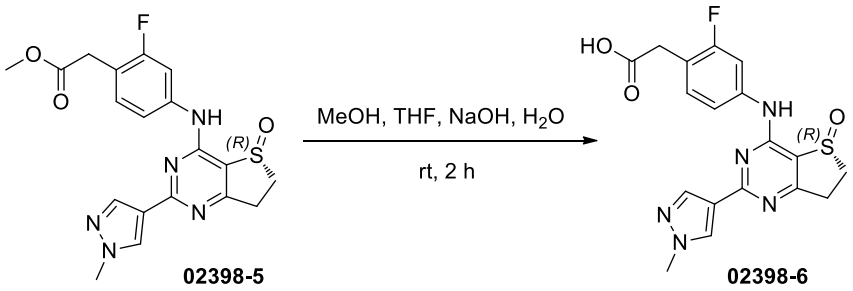
02398-4 02398-5

To a solution of (R)-2-(4-((2-chloro-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (570 mg, 1.54 mmol) and 1-methyl-1H-pyrazole-4-boronic acid (233 mg, 1.85 mmol) in 1,4-dioxane/water (10 mL, v/v 5:1), K_2CO_3 (394 mg, 3.08 mmol) and $Pd(dppf)Cl_2$ (108 mg, 0.15 mmol) were added at 90°C under nitrogen atmosphere. The mixture was stirred at 90°C under nitrogen atmosphere for 5 hours. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH = 1:0 to 20:1, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a yellow solid product (311 mg, 49% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{18}FN_5O_3S]$ $[M+H]^+$: 416.1; found: 415.8

2.6

(R)-2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid(02398-6)

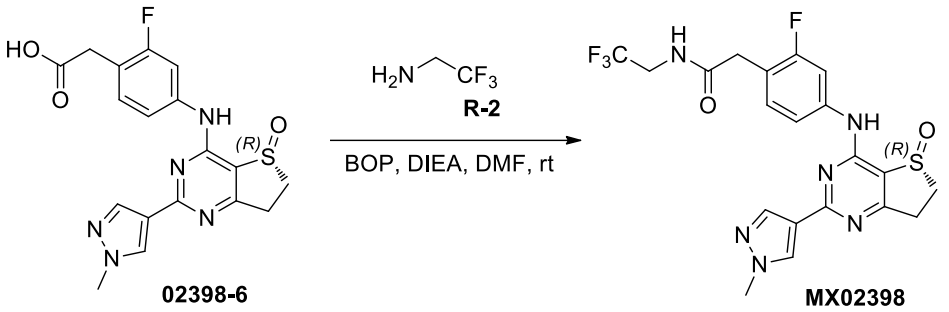


To a solution of (R)-2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid methyl ester (311 mg, 0.75 mmol) in MeOH/THF (6 mL, v/v 1:1), 2N NaOH aqueous solution was added at room temperature to adjust the pH to 12. The mixture was stirred at room temperature under nitrogen atmosphere for 2 hours. After the starting material was consumed, the pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated, and the crude product was purified by reversed-phase column chromatography ($MeCN/H_2O$ = 1:9 to 11:9, C-18 column, 50 mL/min, UV 214) to afford a white solid product (139 mg, 46% yield).

ESI-MS *m/z* calcd for $[C_{18}H_{16}FN_5O_3S]$ $[M+H]^+$: 402.1; found: 401.8

2.7

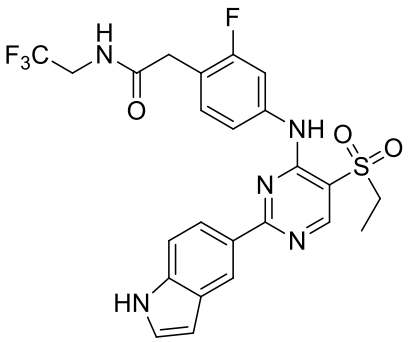
(R)-2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)-N-(2,2, 2-trifluoroethyl)acetamide(MX02398)



To a solution of (R)-2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid (20 mg, 0.05 mmol) in DMF (1 mL), 2,2,2-trifluoroethylamine (10 mg, 0.10 mmol), DIPEA (13 mg, 0.10 mmol), and BOP (22 mg, 0.05 mmol) were added at room temperature. The mixture was stirred at room temperature for 1 hour until the starting material was consumed. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (3.14 mg, 13% yield).

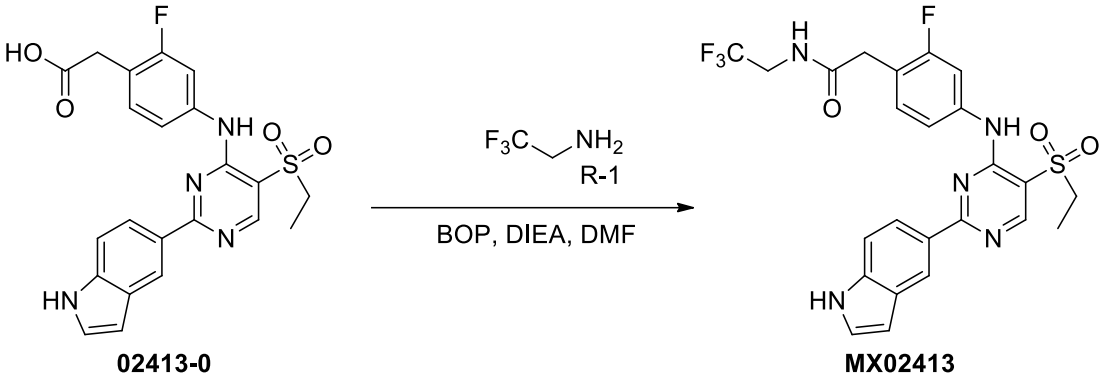
ESI-MS *m/z* calcd for $[C_{20}H_{18}F_4N_6O_2S]$ $[M+H]^+$: 483.1; found: 482.5

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.77 (t, J = 6.0 Hz, 1H), 8.32 (s, 1H), 7.95 (s, 1H), 7.71 – 7.63 (m, 2H), 7.34 (t, J = 8.8 Hz, 1H), 3.99 – 3.90 (m, 5H), 3.73 – 3.65 (m, 1H), 3.58 (s, 2H), 3.44 – 3.37 (m, 1H), 3.31 – 3.24 (m, 1H), 3.13 – 3.08 (m, 1H).



MX02413

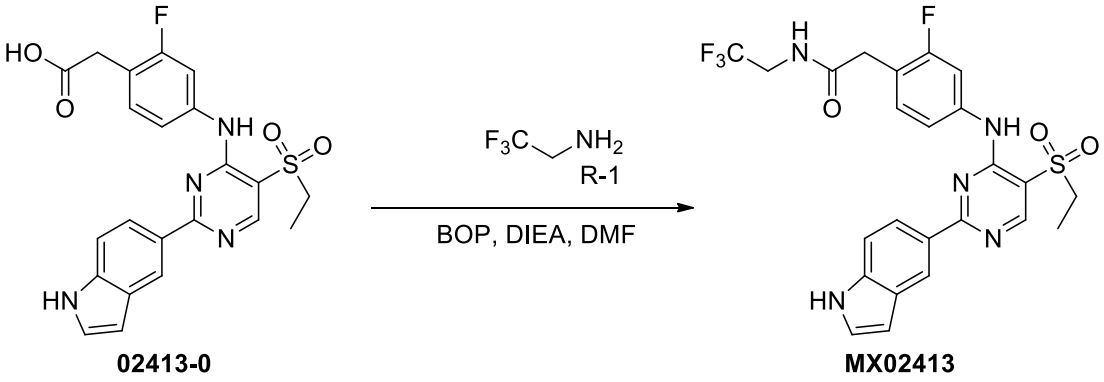
1. Synthetic scheme:



2. Experimental section:

2.1

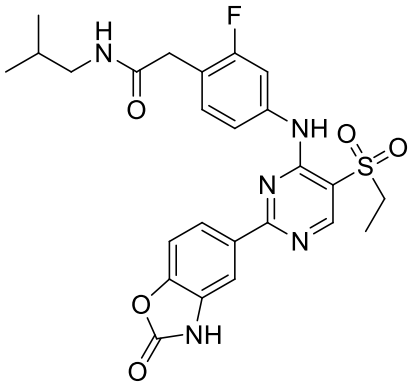
2-(4-((5-(Ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-(2,2,2-trifluoroethyl)acetamide(MX02413)



To a solution of 2-(4-(((5-(ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (20 mg, 0.044 mmol) and 2,2,2-trifluoroethylamine (13.1 mg, 0.132 mmol) in DMF (3 mL), BOP (38.9 mg, 0.088 mmol) and DIPEA (17.1 mg, 0.132 mmol) were added at room temperature. The mixture was stirred at room temperature for 16 hours and then filtered. The filtrate was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (9.69 mg, 41.1% yield).

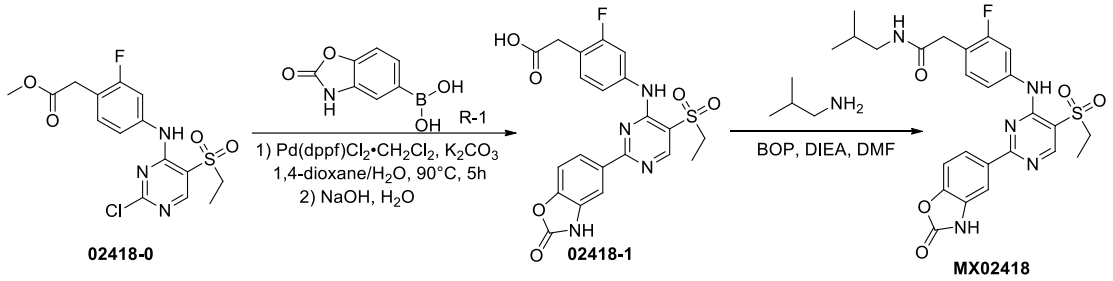
ESI-MS *m/z* calcd for $[C_{24}H_{21}F_4N_5O_3S]$ $[M+H]^+$:536.1; found:535.9

^1H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 9.12 (s, 1H), 8.83 – 8.78 (m, 2H), 8.65 (s, 1H), 8.13 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.78 (dd, *J* = 12.0, 2.0 Hz, 1H), 7.51 – 7.38 (m, 4H), 6.57 (s, 1H), 3.98 – 3.94 (m, 2H), 3.63 (s, 2H), 3.56 – 3.51 (q, *J* = 7.2Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).



MX02418

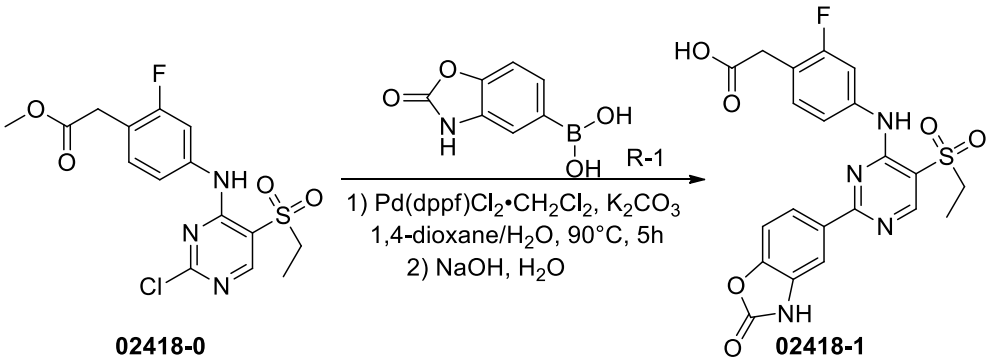
1. Synthetic scheme:



2. Experimental section:

2.1

2-(4-((5-(Ethylsulfonyl)-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(02418-1)



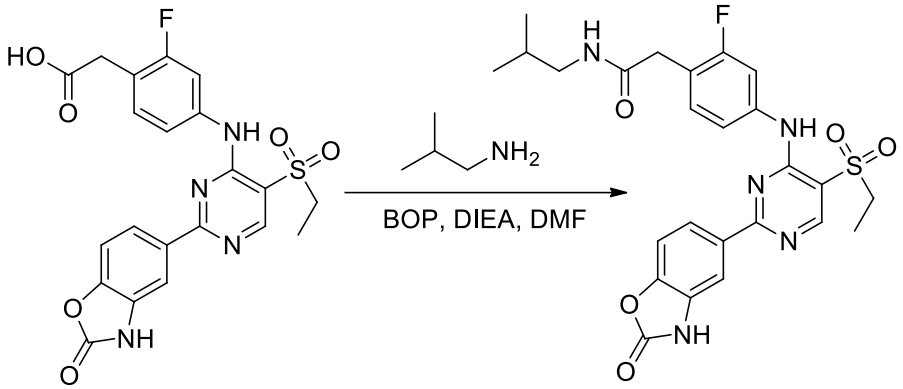
To a solution of 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (60 mg, 0.155 mmol) in 1,4-dioxane/water (10 mL, v/v 4:1), (2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)boronic acid (41.5 mg, 0.232 mmol), K_2CO_3 (64.1 mg, 0.464 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (19 mg, 0.023 mmol) were added at room temperature. The mixture was heated to 90°C and stirred under nitrogen atmosphere for 5 hours. After cooling to room temperature, the reaction mixture was adjusted to pH 12 with 2N NaOH aqueous solution. The reaction mixture was stirred for 16 hours, and then adjusted to neutral

with 1N HCl aqueous solution. After concentration, the crude product was purified by reversed-phase column chromatography (MeCN/H_2O = 0% to 30%, C-18 column, 40 g, 40 mL/min, UV 254) to afford a yellow solid product (21 mg, 28.7% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{17}FN_4O_6S]$ $[M+H]^+$: 473.1; found: 473.0

2.2

2-(4-((5-(Ethylsulfonyl)-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutylethanamide(MX02418)

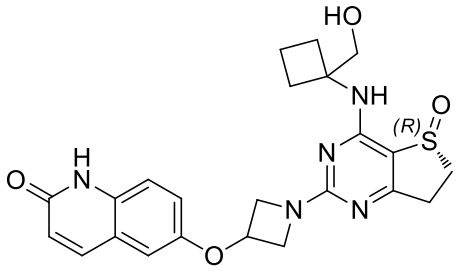


02418-1 MX02418

To a solution of 2-(4-(((5-(ethylsulfonyl)-2-(2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (21 mg, 0.044 mmol) and isobutylamine (9.8 mg, 0.133 mmol) in DMF (3 mL), BOP (39.3 mg, 0.089 mmol) and DIPEA (23 mg, 0.178 mmol) were added at room temperature. The mixture was stirred at room temperature for 16 hours, and then the reaction mixture was filtered. The filtrate was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (2.31 mg, 9.9% yield).

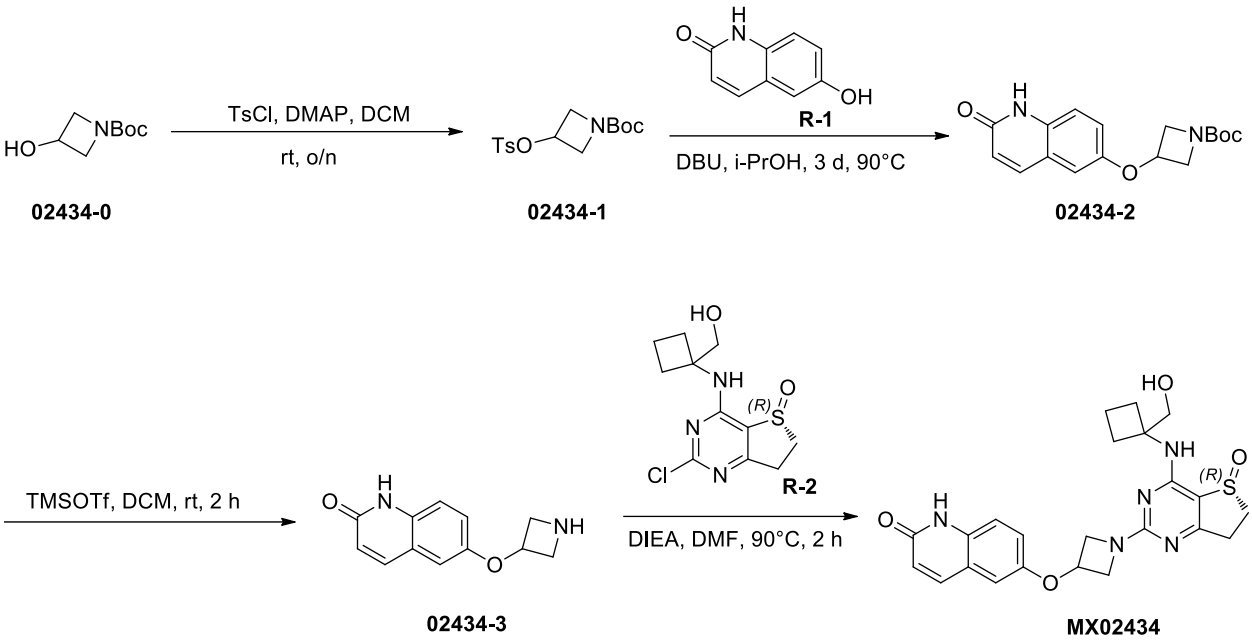
ESI-MS *m/z* calcd for $[C_{25}H_{26}FN_5O_5S]$ $[M+H]^+$:528.2; found:527.8

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.79 (s, 1H), 8.08 – 8.06 (m, 2H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.63 (dd, *J* = 8.0 , 1.6 Hz, 1H), 7.41 – 7.37 (m, 3H), 3.55 – 3.52 (m, 4H), 2.93 – 2.90 (m, 2H), 1.74 – 1.67 (m ,1H), 1.25 (t, *J* = 7.6 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 6H).



MX02434

1. Synthetic scheme:

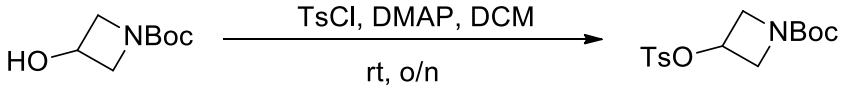


02434-0 02434-1 02434-2

02434-3 MX02434

2. Experimental section:

2.1 3-(p-Toluenesulfonyl-oxy)azetidine-1-carboxylic acid tert-butyl ester (02434-1)



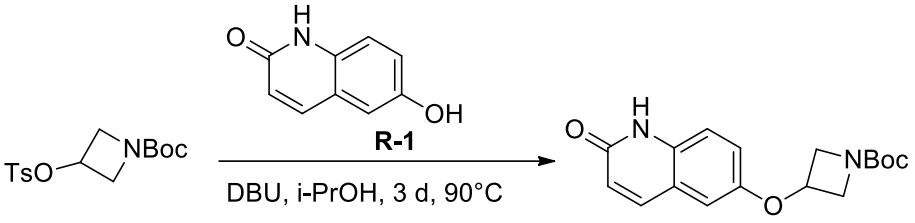
02434-0 **02434-1**

To a solution of 1-(tert-butyl carbamate)-3-hydroxyazetidine (3.2 g, 18.5 mmol) in anhydrous DCM (50 mL), TsCl (5.27 g, 27.74 mmol) and DMAP (4.51 g, 37 mmol) were added at room temperature. The mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl solution (100 mL) at 0 °C and extracted with ethyl acetate (EA, 100 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated, and purified by column chromatography (EA/hexane = 0:1 to 1:9, silica gel CS 40 g, 40 mL/min, silica gel, UV 254) to afford a colorless oily product (6.0 g, 99% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{21}NO_5S]$ $[M-56+H]^+$: 272.1; found: 272.2

2.2

tert-Butyl 3-((2-oxo-1,2-dihydroquinolin-6-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester(02434-2)



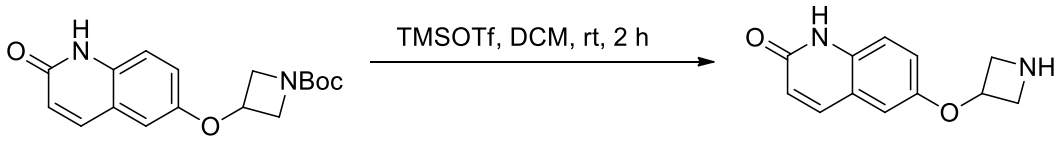
02434-1 **02434-2**

To a solution of 3-(p-toluenesulfonyloxy)azetidine-1-carboxylic acid tert-butyl ester (1 g, 3.06 mmol) and 2,6-dihydroxyquinoline (492 mg, 3.06 mmol) in isopropanol (10 mL), DBU (930 mg, 6.12 mmol) was added at room temperature. The reaction mixture was stirred at 90°C for 3 days. The solvent was removed under reduced pressure. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (EA, 50 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/hexane = 0:1 to 50:1, silica gel CS 40 g, 50 mL/min, silica gel, UV 254) to afford a yellow solid product (227 mg, 23% yield).

ESI-MS *m/z* calcd for $[C_{17}H_{20}N_2O_4]$ $[M+H]^+$: 317.1; found: 316.8

2.3

6-(Aziridin-3-yloxy)quinolin-2(1H)-one(02434-3)



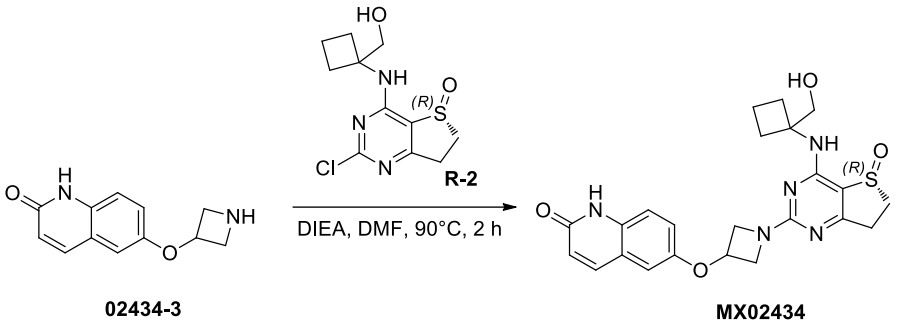
02434-2 **02434-3**

To a solution of 1-(tert-butyl)-3-((2-oxo-1,2-dihydroquinolin-6-yl)oxy)azetidine-1-carboxylate (20 mg, 0.06 mmol) in DCM (3 mL), TMSOTf (0.5 mL) was added at room temperature. The mixture was stirred at room temperature under nitrogen atmosphere for 2 hours until the starting material was consumed. The mixture was concentrated under reduced pressure to dryness, affording a white solid product (13 mg, 95% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{12}N_2O_2]$ $[M+H]^+$: 217.1; found: 217.0

2.4

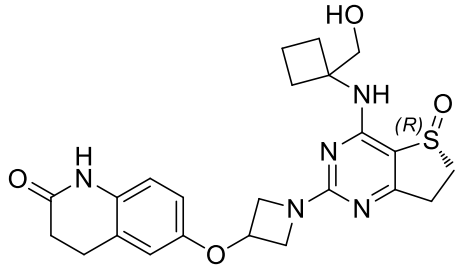
(R)-6-((1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)quinoline-2 (1H)-ketone(MX02434)



To a solution of 6-(azetidin-3-yloxy)quinolin-2(1H)-one (14 mg, 0.06 mmol) in DMF (2 mL), (R)-2-chloro-4-((1-hydroxymethylcyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (18 mg, 0.06 mmol) and DIPEA (15 mg, 0.12 mmol) were added at 90°C under nitrogen atmosphere. The mixture was stirred for 2 hours until the starting material was consumed. The reaction mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (7.08 mg, 16% yield).

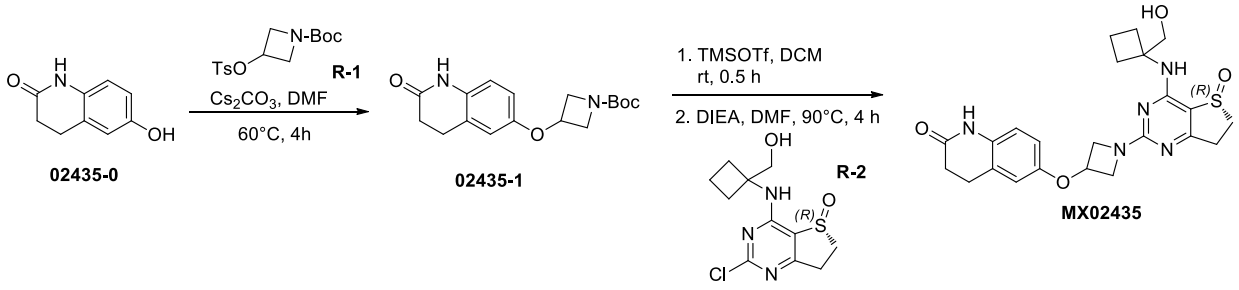
ESI-MS *m/z* calcd for $[C_{23}H_{25}N_5O_4S]$ $[M+H]^+$: 468.2; found: 467.6

^{1}H NMR (400 MHz,DMSO-d_6) δ 11.67 (s, 1H), 7.86 (d, *J* = 9.6 Hz, 1H), 7.48 (s, 1H), 7.27 (d, *J* = 9.2 Hz, 1H), 7.17 – 7.12 (m, 2H), 6.51 (d, *J* = 9.2 Hz, 1H), 5.15 – 5.10 (m, 1H), 4.85 (t, *J* = 5.6 Hz, 1H), 4.48 (dd, *J* = 10.0, 6.4 Hz, 2H), 4.03 – 3.86 (m, 2H), 3.74 – 3.66 (m, 2H), 3.45 –3.36 (m, 1H), 3.25 –3.18 (m, 1H), 2.97 –2.85 (m, 2H), 2.38 –2.25 (m, 2H), 2.15 – 2.11 (m, 2H), 1.82 –1.68 (m, 2H).



MX02435

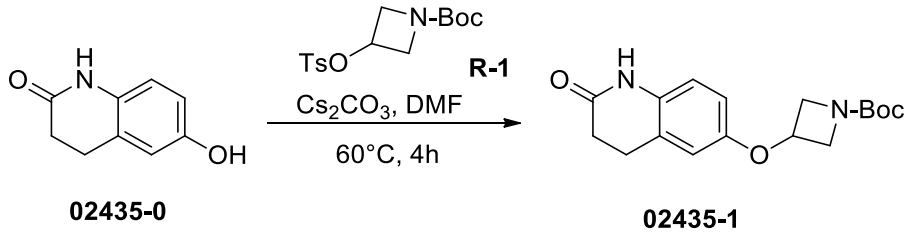
1. Synthetic scheme:



2. Experimental section:

2.1

tert-Butyl-3-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy)azetidine-1-carboxylate(02435-1)

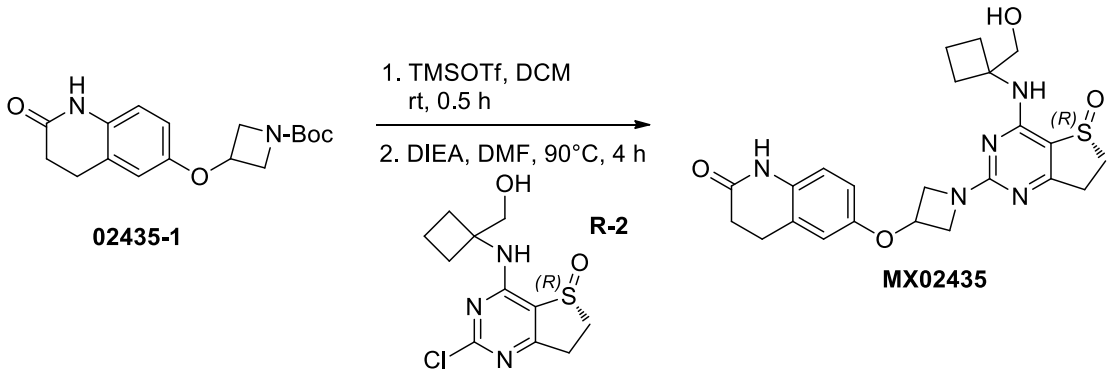


To a solution of 6-hydroxy-3,4-dihydroquinolin-2(1H)-one (200 mg, 1.22 mmol) and 3-(p-toluenesulfonyloxy)azetidine-1-carboxylic acid tert-butyl ester (400 mg, 1.22 mmol) in DMF (10 mL), Cs_2CO_3 (798 mg, 2.45 mmol) was added at room temperature. The mixture was stirred at 60°C for 4 hours. Water (20 mL) was added and the mixture was extracted with ethyl acetate (EA, 40 mL) twice. The combined organic layers were washed with saturated saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/DCM = 0:1 to 1:1, silica gel CS 12 g, 30 mL/min, silica gel, UV 254) to afford a white solid product (288 mg, 64.5% yield).

ESI-MS *m/z* calcd for $[C_{17}H_{22}N_2O_4]$ $[M-56+H]^+$: 263.2; found: 263.2

2.2

(R)-6-((1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)-3,4-dihydroquinoline-2 (1H)-ketone (MX02435)

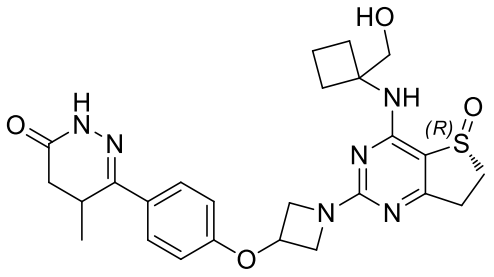


To a solution of 3-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (13 mg, 0.041 mmol) in DCM (2 mL), TMSOTf (14 mg, 0.061 mmol) was added at room temperature. The mixture was stirred at room temperature for 30 minutes. After the reaction, the pH of the mixture was adjusted to 7 with TEA (0.02 mL). The reaction mixture was concentrated under reduced pressure to afford the crude product. To a solution of the crude product in DMF (2 mL), (R)-2-chloro-4-[(1-hydroxymethylcyclobutyl)amino]-6,7-

dihydrothieno[3,2-d]pyrimidin-5-oxide (9.4 mg, 0.033 mmol) and DIPEA (11 mg, 0.082 mmol) were added at room temperature. The mixture was stirred at 90°C for 4 hours. The reaction mixture was concentrated under reduced pressure to afford the crude product. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (9 mg, 58.2% yield).

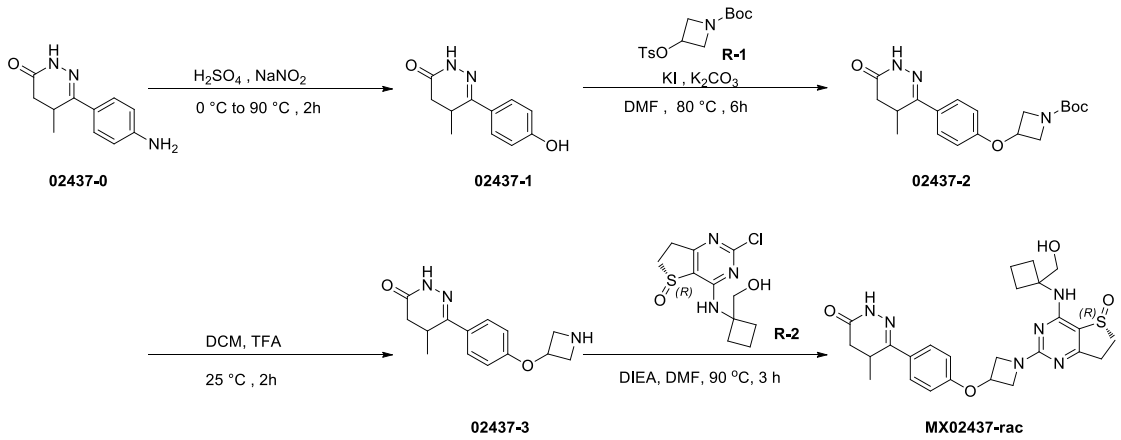
ESI-MS *m/z* calcd for $[C_{23}H_{27}N_5O_4S]$ $[M+H]^+$: 470.2; found: 469.9

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 7.47 (s, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.67 (dd, J = 8.8, 2.8 Hz, 1H), 5.05 – 5.01 (m, 1H), 4.85 (t, J = 5.6 Hz, 1H), 4.44 – 4.40 (m, 2H), 3.89 – 3.85 (m, 2H), 3.70 – 3.68 (m, 2H), 3.43 – 3.35 (m, 1H), 3.30 – 3.17 (m, 1H), 2.96 – 2.82 (m, 4H), 2.46 – 2.39 (m, 2H), 2.35 – 2.25 (m, 2H), 2.15 – 2.10 (m, 2H), 1.79 – 1.72 (m, 2H).



MX02437-rac

1. Synthetic scheme:

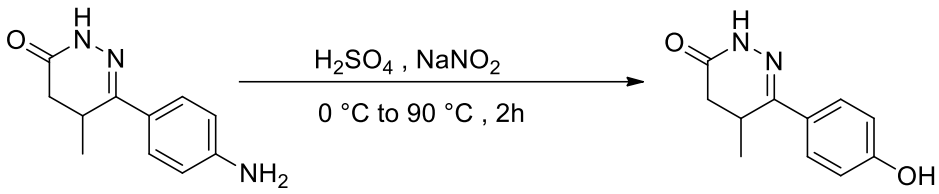


02437-0 02437-1 02437-2 02437-3 MX02437-rac

2. Experimental section:

2.1

6-(4-hydroxyphenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one(02437-1)



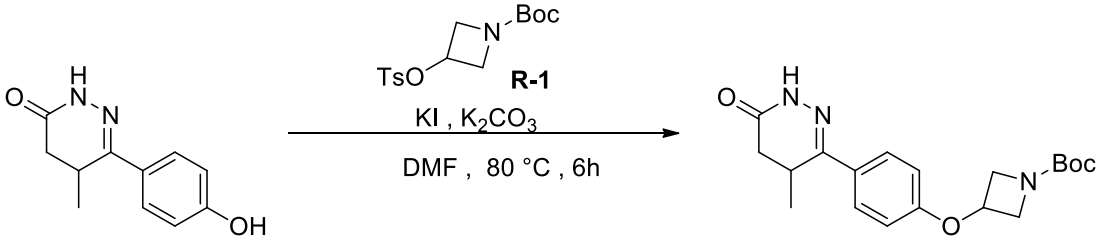
02437-0 **02437-1**

To a solution of 6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (500 mg, 2.461 mmol) in water (5 mL), sulfuric acid (1 g, 10.20 mmol) was added at 0°C. The mixture was stirred at 0°C. Aqueous sodium nitrite solution (5 mL, 190 mg, 2.75 mmol) was slowly added dropwise to the reaction mixture, and the mixture was stirred for 20 minutes. The mixture was slowly warmed to 90°C over 20 minutes. The mixture was poured into water (30 mL), filtered, and dried to afford the crude product. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a dark brown solid product (220 mg, 43.82% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{12}N_2O_2]$ $[M+H]^+$:205.0; found: 205.0

2.2

tert-Butyl-3-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy)azetidine-1-carboxylate(02437-2)



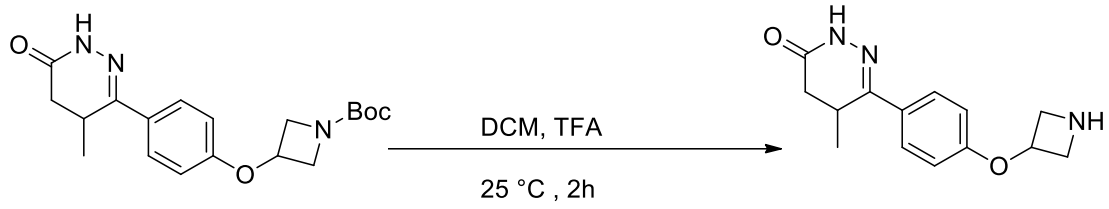
02437-1 **02437-2**

To a solution of 6-(4-hydroxyphenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (220 mg, 1.07 mmol) and 3-(p-toluenesulfonyloxy)azetidine-1-carboxylic acid tert-butyl ester (350 mg, 1.07 mmol) in DMF (10 mL), K_2CO_3 (442 mg, 3.21 mmol) and KI (35.52 mg, 0.214 mmol) were added at 0°C. The mixture was stirred at 80°C for 6 hours. The mixture was poured into water (50 mL) and extracted with ethyl acetate (EA, 30 mL) twice. The combined organic layers were washed with saturated saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0:1 to 80:20, silica gel CS 12 g, 20 mL/min, silica gel, UV 254) to afford a white solid product (208 mg, 53.74% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{25}N_3O_4]$ $[M+H]^+$:360.2; found: 360.4

2.3

6-(4-(Azabicyclo[3.3.1]hept-3-yloxy)phenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one(02437-3)

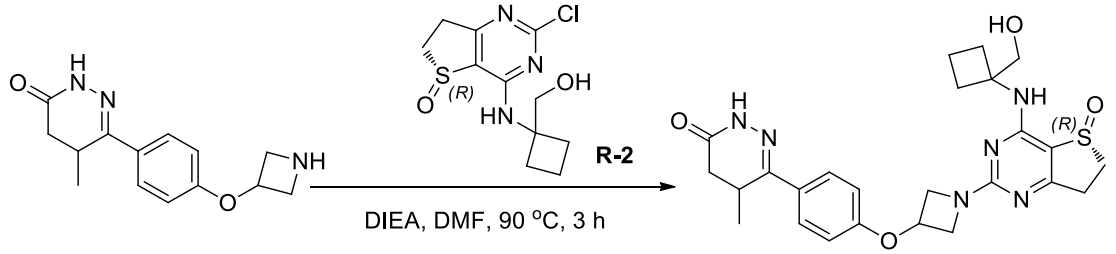


02437-2 02437-3

To a solution of 3-(4-((4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)oxy)phenoxy)azetidine-1-carboxylic acid tert-butyl ester (70 mg, 2.508 mmol) in DCM (5 mL) was added TFA (0.5 mL) at 25°C. The mixture was stirred at 25°C for 2 hours. The solvent was removed under reduced pressure. The crude product (87 mg) was used directly for the next step.

ESI-MS *m/z* calcd for $[C_{14}H_{17}N_3O_2]$ $[M+H]^+$:260.2; found: 260.0

2.46-(4-((1-((R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)phenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one(MX02437-rac)



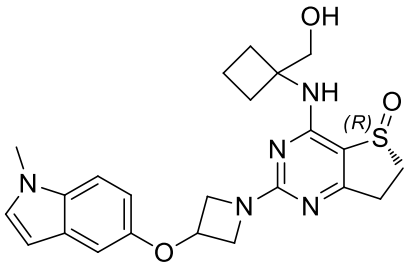
02437-3 MX02437-rac

To a solution of 6-(4-(azetidin-3-yloxy)phenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (87 mg, 0.335 mmol) and (R)-2-chloro-4-((1-hydroxymethylcyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (96.35 mg, 0.335 mmol) in DMF (5 mL) was added DIPEA (43.29 mg, 1.340 mmol) at room temperature. The mixture was stirred at 90°C for 3 hours, cooled to room temperature, and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (40.89 mg, 23.92% yield).

ESI-MS *m/z* calcd for $[C_{25}H_{30}N_6O_4S]$ $[M+H]^+$:511.2; found: 511.3

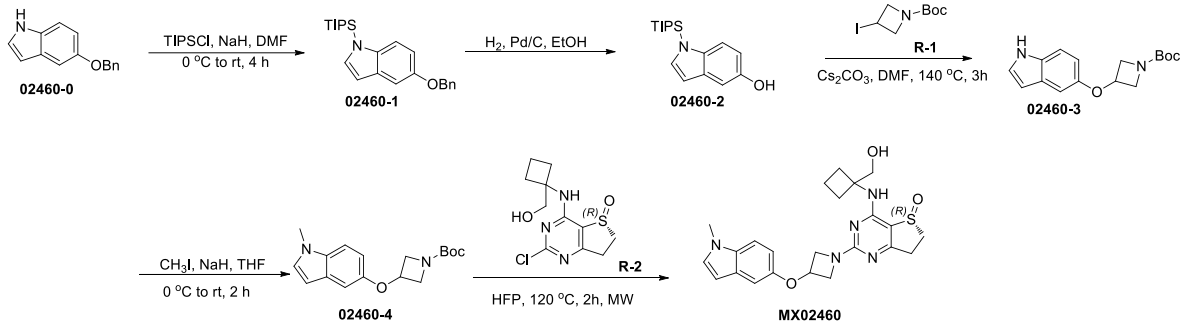
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.75 (d, J = 9.2, 2H), 7.47 (s, 1H), 6.94 (d, J = 8.8, 2H), 5.20 – 5.15 (m, 1H), 4.84 (t, J = 5.6 Hz, 1H), 4.49 – 4.45 (m, 2H), 4.02 – 3.87 (m, 2H), 3.70 – 3.67 (m, 2H), 3.45 – 3.36 (m, 2H), 3.27 – 3.18 (m, 1H), 2.97 – 2.85 (m, 2H),

2.70 – 2.64 (m, 1H), 2.38 – 2.22 (m, 3H), 2.15 – 2.10 (m, 2H), 1.82 – 1.67 (m, 2H), 1.07 (d, *J* = 7.2 H, 3H).



MX02460

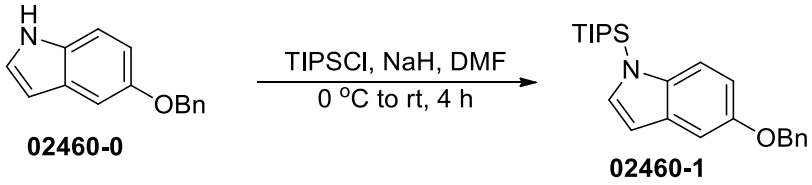
1. Synthetic scheme:



2. Experimental section:

2.1

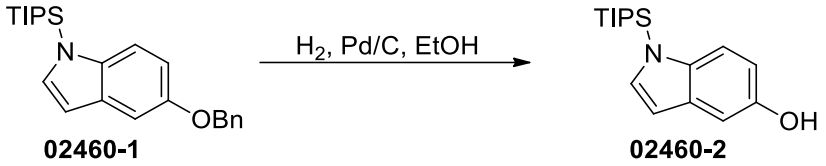
5-(Benzyloxy)-1-(triisopropylsilyl)-1H-indole(0206-1)



To a solution of 5-(benzyloxy)-1H-indole (3 g, 13.45 mmol) in anhydrous THF (20 mL) was added a solution of NaH (60%, 699 mg, 17.48 mmol) in THF (20 mL) dropwise at 0°C. The mixture was allowed to warm to room temperature over 30 minutes, followed by dropwise addition of TIPSCl (3.37 g, 17.48 mmol) at 0°C within 5 minutes. The reaction mixture was then slowly warmed to room temperature and stirred for 4 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) at 0°C and extracted with diethyl ether (Et_2O, 15 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/hexane = 0:1 to 1:9, silica gel CS 40 g, 40 mL/min, silica gel, UV 254) to afford a white solid product (3.2 g, 62.69% yield).

2.2

1-(Triisopropylsilyl)-1H-indole-5-ol(02060-2)



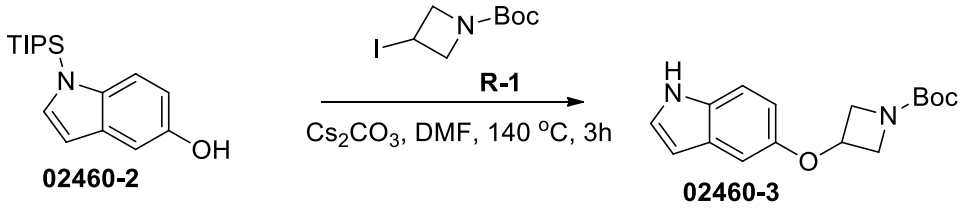
02460-1 02460-2

To a solution of 5-(benzyloxy)-1-(triisopropylsilyl)-1H-indole (3.2 g, 8.43 mmol) in EtOH (40 mL) was added Pd/C (120 mg) at room temperature. The mixture was stirred under hydrogen atmosphere overnight. The mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to afford a colorless oily product (2.3 g, 94.3% yield).

ESI-MS *m/z* calcd for $[C_{17}H_{27}NOSi]$ $[M+H]^+$: 290.2; found: 290.2

2.3

tert-Butyl 3-((1H-indol-5-yl)oxy)azetidine-1-carboxylate(02060-3)



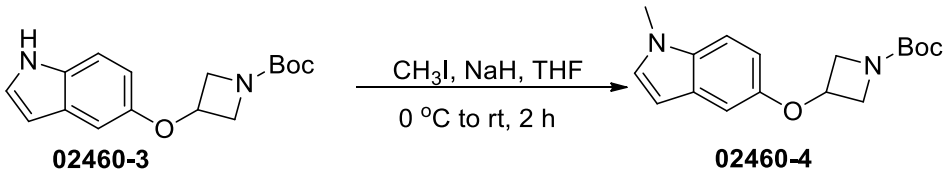
02460-2 02460-3

To a solution of 1-(triisopropylsilyl)-1H-indol-5-ol (2.67 g, 9.22 mmol) and Cs_2CO_3 (9.0 g, 27.67 mmol) in DMF (50 mL) was added 3-iodoazetidine-1-carboxylic acid tert-butyl ester (3.1 g, 11.07 mmol) at room temperature. The reaction mixture was stirred at 140°C for 3 hours. The solvent was removed under reduced pressure. Water (150 mL) was added, and the mixture was extracted with ethyl acetate (EA, 75 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/hexane = 0:1 to 50:50, silica gel CS 40 g, 50 mL/min, silica gel, UV 254) to afford a yellow solid product (480 mg, 81.5% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{20}N_2O_3]$ $[M+H]^+$: 289.2; found: 289.1

2.4

tert-Butyl 3-((1-methyl-1H-indol-5-yl)oxy)azetidine-1-carboxylate(02460-4)



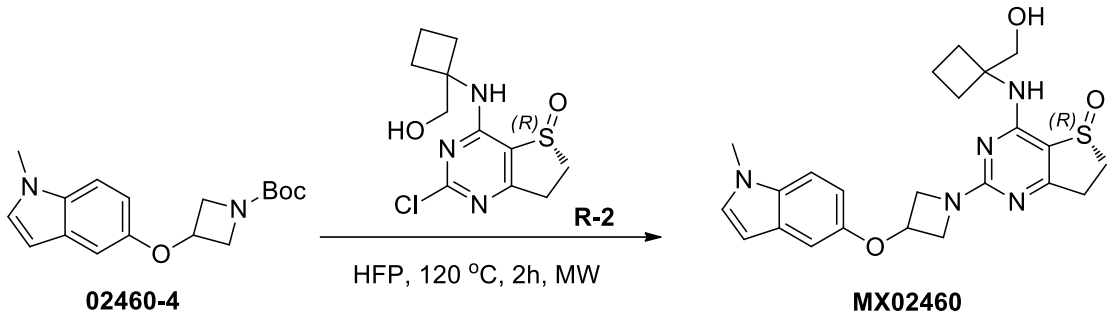
02460-3 02460-4

To a solution of 3-((1H-indol-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (150 mg, 0.52 mmol) in anhydrous THF (10 mL) was added a solution of NaH (60%, 699 mg, 0.67 mmol) in THF (20 mL) dropwise at 0°C. The reaction mixture was allowed to warm to room temperature over 30 minutes, followed by dropwise addition of MeI (88 mg, 0.62 mmol) at 0°C. The resulting mixture was slowly warmed to room temperature and stirred for 2 hours. Then, saturated NH_4Cl solution (20 mL) was added at 0°C, and the mixture was extracted with diethyl ether (Et_2O, 15 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/hexane = 0:1 to 75:25, silica gel CS 20 g, 40 mL/min, silica gel, UV 254) to afford a yellow solid product (480 mg, 81.5% yield).

ESI-MS *m/z* calcd for $[C_{17}H_{22}N_2O_3]$ $[M-56+H]^+$: 247.2; found: 247.2

2.5

(R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(3-((1-methyl-1H-indol-5-yloxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02460)



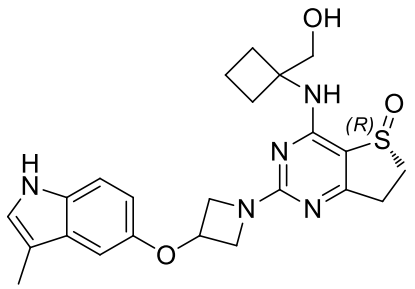
02460-4 **MX02460**

A solution of 3-((1-methyl-1H-indol-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (40 mg, 0.13 mmol) and (R)-2-chloro-4-((1-hydroxymethylcyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (37 mg, 0.13 mmol) in HFP (2 mL) was stirred at 120°C under microwave condition for 2 hours. After the reaction was complete, the mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (8.35 mg, 14.2% yield).

ESI-MS *m/z* calcd for $[C_{23}H_{27}N_5O_3S]$ $[M+H]^+$: 454.2; found: 454.3

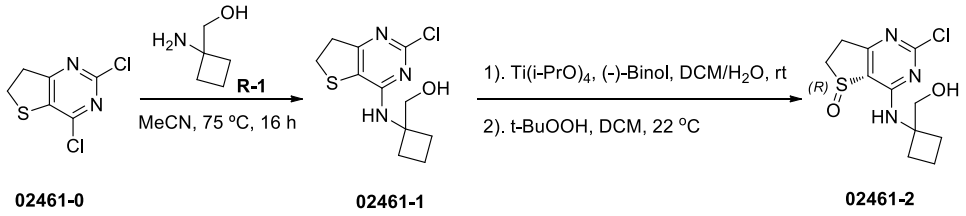
^1H NMR (400 MHz,DMSO-d_6) δ 7.44 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 2.8 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 8.8, 2.4 Hz, 1H), 6.33 – 6.32 (m, 1H), 5.12 – 5.07 (m, 1H), 4.84 (t, J = 5.6 Hz, 1H), 4.47 – 4.43 (m, 2H), 4.02 – 3.85 (m, 2H), 3.75 (s, 3H), 3.74 –3.67 (m, 2H), 3.45 –3.37 (m, 1H), 3.25 –3.18 (m, 1H), 2.97 –2.84 (m, 2H), 2.38 –2.25

(m, 2H), 2.14 –2.10 (m, 2H), 1.81 –1.67 (m, 2H).

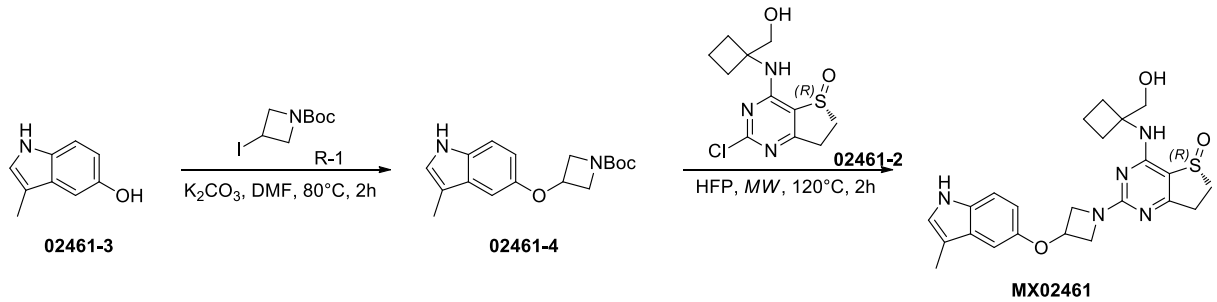


MX02461

1. Synthetic scheme:



02461-0 02461-1 02461-2

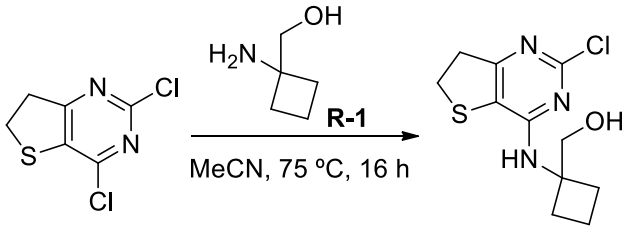


02461-3 02461-4 MX02461

2. Experimental section:

2.1

(1-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)cyclobutyl)methanol(02461-1)



02461-0 02461-1

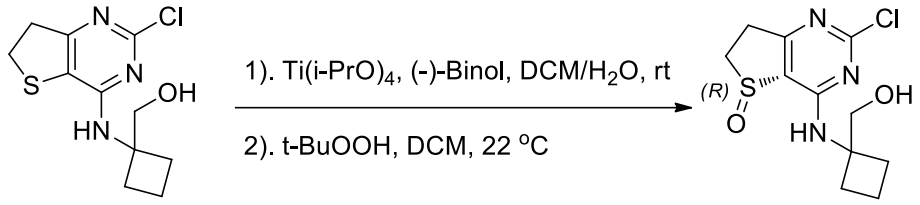
To a solution of 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidine (6.64 g, 32.07 mmol) in MeCN (50 mL) were added 1-aminocyclobutyl methanol (3.24 g, 32.07 mmol) and TEA (20 mL)room temperature. The mixture was stirred at 75°C for 16 hours. The solvent was removed

under reduced pressure. The crude product was purified by column chromatography (EA/DCM = 0:1 to 60:40, silica gel CS 120 g, 50 mL/min, silica gel, UV 254) to afford a yellow solid product (4.01 g, 46.1% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{14}ClN_3OS]$ $[M+H]^+$: 272.1; found: 272.1

2.2

(R)-2-Chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (02461-2)



02461-1 **02461-2**

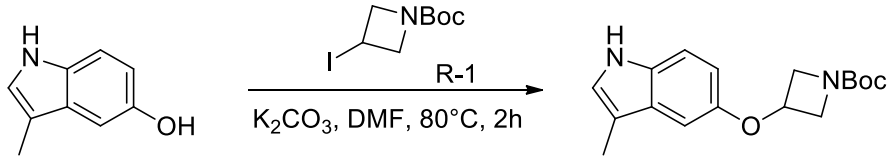
To a solution of (1-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)cyclobutyl)methanol (3.5 g, 12.88 mmol) and S-1,1'-binaphthol (369.0 mg, 1.288 mmol) in DCM (60 mL) were added titanium tetraisopropoxide (182 mg, 0.64 mmol) and water (232 mg, 12.88 mmol) at room temperature. The mixture was stirred at room temperature for 1 hour. Then, 70% tert-butyl hydroperoxide aqueous solution (2 g, 14.17 mmol) was added all at once. The mixture was stirred at room temperature for 2 hours. Water (50 mL) was added, and the mixture was extracted with DCM (60 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH = 1:0 to 10:1, silica gel CS 80 g, 50 mL/min, silica gel, UV 254) to afford a yellow solid product (3.50 g, 94.6% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{14}ClN_3O_2S]$ $[M+H]^+$: 288.0; found: 288.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 4.89 (t, J = 5.6 Hz, 1H), 3.74 – 3.66 (m, 2H), 3.61 – 3.52 (m, 1H), 3.38 – 3.30 (m, 1H), 3.16 – 3.12 (m, 1H), 3.05 – 2.99 (m, 1H), 2.32 – 2.17 (m, 4H), 1.81 – 1.71 (m, 2H).

2.3

tert-Butyl 3-(3-methyl-1H-indol-5-yloxy)azetidine-1-carboxylate(02461-4)



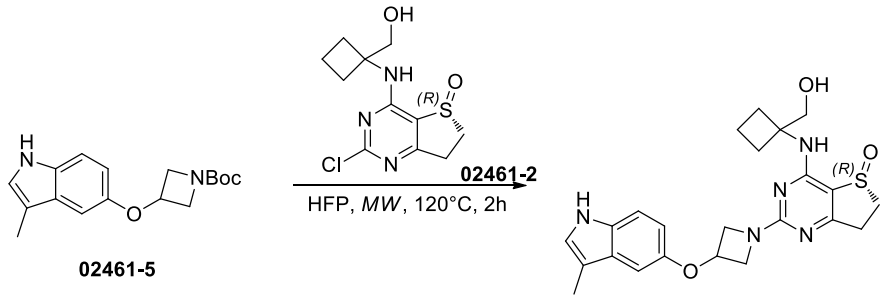
02461-3 **02461-4**

To a solution of 3-methyl-1H-indol-5-ol (300 mg, 2.038 mmol) in DMF (5 mL) were added 3-iodoazetidine-1-carboxylic acid tert-butyl ester (577.1 mg, 2.038 mmol) and K_2CO_3 (422.6 mg, 3.058 mmol) at 80°C. The mixture was stirred at 80°C for 2 hours. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (EA, 25 mL) twice. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 20:80, silica gel CS 20 g, 25 mL/min, silica gel, UV 254) to afford a white solid product (223 mg, 36.2% yield).

ESI-MS m/z calcd for $[C_{17}H_{22}N_2O_3]$ $[M-56+H]^+$:247.2; found:247.2

2.4

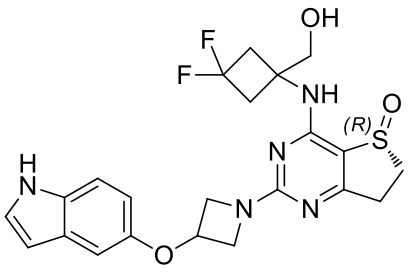
(R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(3-((3-methyl-1H-indol-5-yloxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine-5-oxide(MX02461)



To a solution of 3-(3-methyl-1H-indol-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (40 mg, 0.132 mmol) in HFP (3 mL) was added (R)-2-chloro-4-((1-hydroxymethylcyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (38.1 mg, 0.132 mmol) at room temperature. The mixture was stirred at 120°C under microwave conditions for 2 hours. After cooling to room temperature, the reaction mixture was concentrated. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (15.86 mg, 26.4% yield).

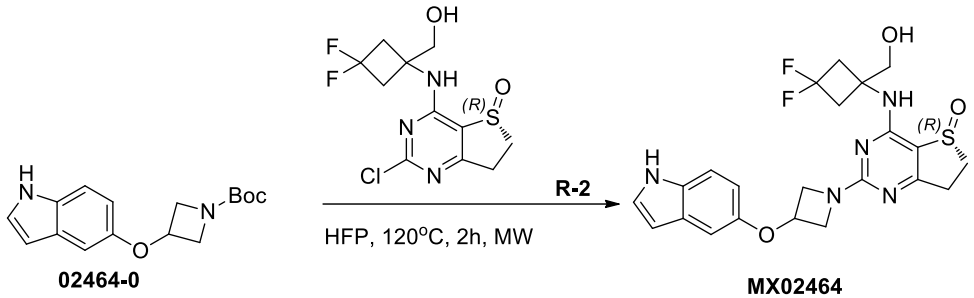
ESI-MS m/z calcd for $[C_{23}H_{27}N_5O_3S]$ $[M+H]^+$:454.2; found:454.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 – 10.61 (m, 1H), 7.45 (s, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.08 (s, 1H), 6.84 (d, J = 2.0 Hz, 1H), 6.70 (dd, J = 8.8, 2.0 Hz, 1H), 5.13 – 5.11 (m, 1H), 4.86 (t, J = 6.0 Hz, 1H), 4.47 – 4.43 (m, 2H), 3.95 – 3.93 (m, 2H), 3.70 – 3.69 (m ,2H), 3.43 – 3.37 (m, 1H), 3.23 – 3.20 (m, 1H), 2.97 – 2.86 (m, 2H), 2.36 – 2.28 (m, 2H), 2.22 (s, 3H), 2.15 – 2.09 (m, 2H), 1.77 – 1.72 (m, 2H).



MX02464

1. Synthetic scheme:

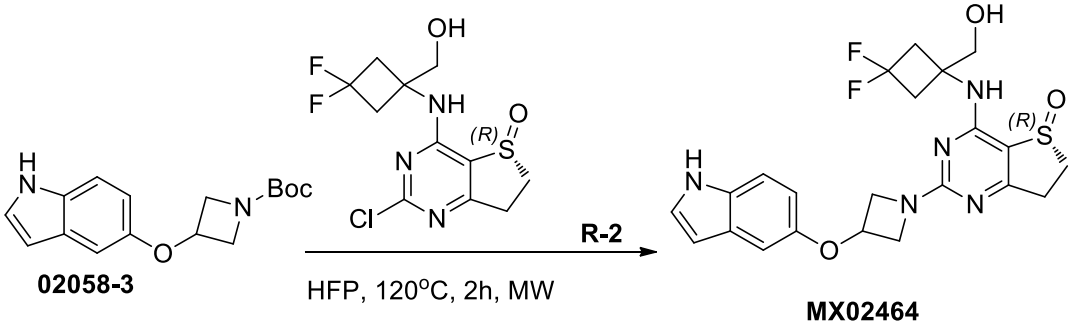


02464-0 **MX02464**

2. Experimental section:

2.1

(R)-2-(3-((1H-indol-5-yl)oxy)azetidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02464)

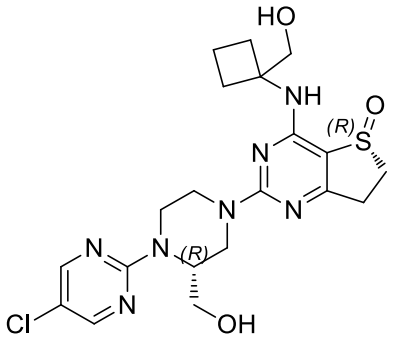


02058-3 **MX02464**

A solution of (R)-2-chloro-4-((3,3-difluoro-1-hydroxymethylcyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (20 mg, 0.062 mmol) and 3-((1H-indol-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (21.3 mg, 0.074 mmol) in HFP (3 mL) was stirred under microwave conditions at 120°C for 2 hours. Water (10 mL) was added to the mixture, and it was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid compound (10.0 mg, 34.0% yield).

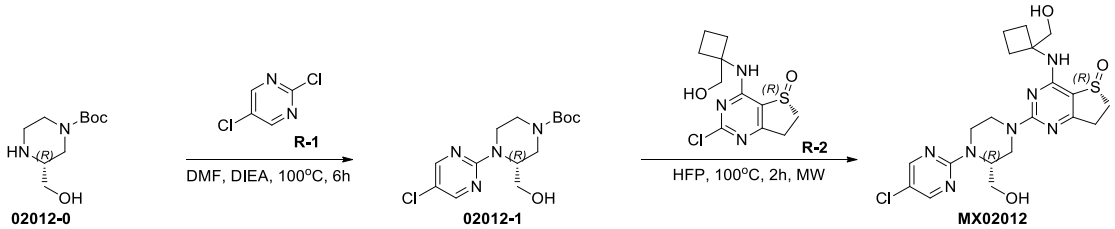
ESI-MS *m/z* calcd for $[C_{22}H_{23}F_2N_5O_3S]$ $[M+H]^+$: 476.2; found: 476.2

^{1}H NMR (400 MHz,DMSO-d_6) δ 10.97 (s, 1H), 7.95 (s, 1H), 7.32 – 7.30 (m, 2H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.35 (t, *J* = 2.4 Hz, 1H), 5.14 – 5.07 (m, 2H), 4.48 – 4.44 (m, 2H), 3.96 – 3.95 (m, 2H), 3.67 – 3.66 (m, 2H), 3.48 – 3.39 (m, 1H), 3.24 – 3.17 (m, 1H), 2.99 –2.83 (m, 6H).



MX02012

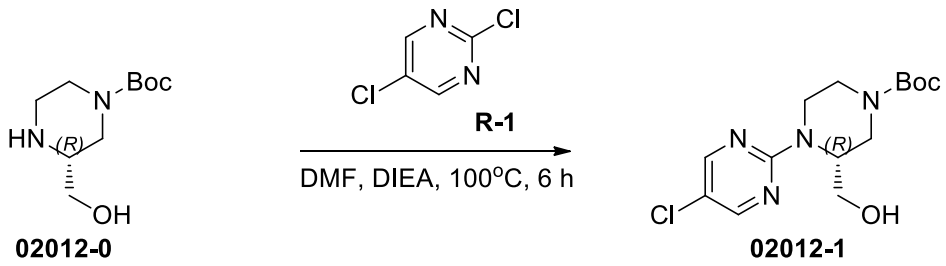
1. Synthetic scheme:



2. Experimental section:

2.1

(R)-4-(5-Chloropyrimidin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylic acid tert-butyl ester(02450-1)



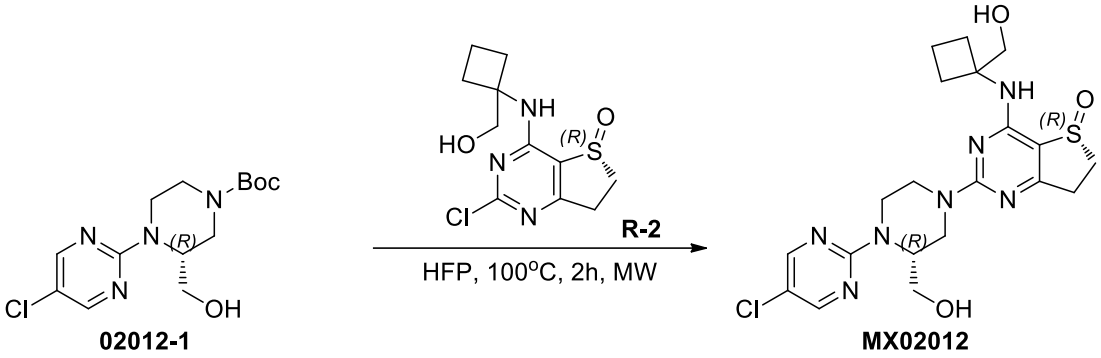
To a solution of (R)-3-(hydroxymethyl)piperazine-1-carboxylic acid tert-butyl ester (500 mg, 2.31 mmol) in DMF (10 mL) were added 2,5-dichloropyrimidine (341 mg, 2.31 mmol) and DIPEA (894 mg, 6.93 mmol) at 100°C under nitrogen atmosphere. The mixture was stirred for 6 hours until the starting material was consumed. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (EA, 20 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column

chromatography (EA/hexane = 0:1 to 2:3, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a yellow oily product (554 mg, 73% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{21}ClN_4O_3]$ $[M+H]^+$: 329.1; found: 329.3

2.2

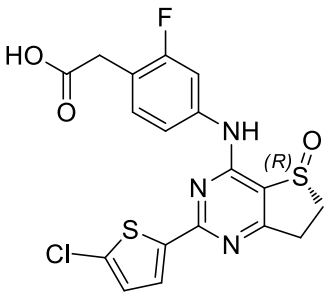
(R)-2-((R)-4-(5-Chloropyrimidin-2-yl)-3- (hydroxymethyl)piperazin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02012)



A solution of (R)-4-(5-chloropyrimidin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylic acid tert-butyl ester (50 mg, 0.15 mmol) and (R)-2-chloro-4-((1-hydroxymethylcyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (43 mg, 0.15 mmol) in HFP (2 mL) was stirred at 120°C under microwave conditions for 2 hours. After the reaction was complete, the mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (8.16 mg, 11.0% yield).

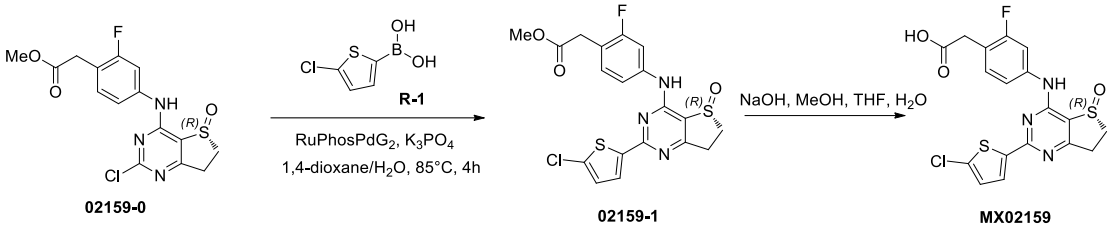
ESI-MS *m/z* calcd for $[C_{20}H_{26}ClN_7O_3S]$ $[M+H]^+$: 480.2; found: 480.2

^{1}H NMR (400 MHz,DMSO-d_6) δ 8.44 (s, 2H), 7.34 (s, 1H), 4.82 (t, J = 5.6 Hz, 1H), 4.73 – 4.38 (m, 5H), 3.72 (d, J = 5.6,Hz, 2H), 3.45 – 3.37 (m, 3H), 3.29 – 3.09 (m, 4H), 2.98 – 2.84 (m, 2H), 2.45 – 2.29 (m, 2H), 2.20 –2.15 (m, 2H), 1.82 –1.70 (m, 2H).



MX02159

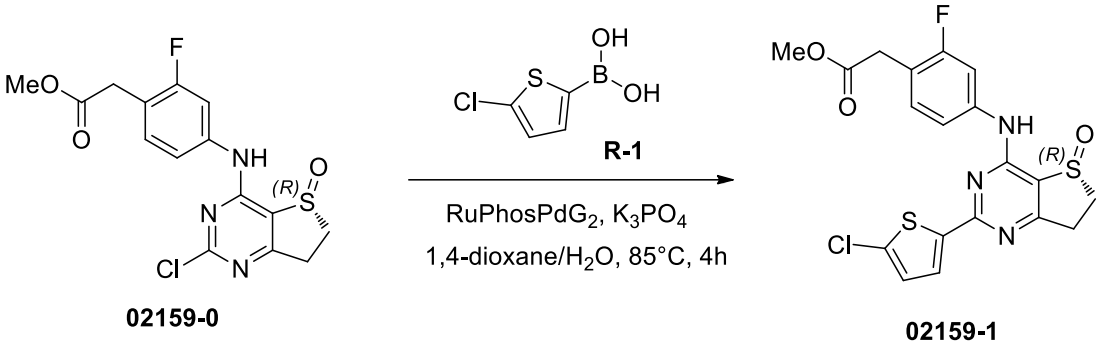
1. Synthetic scheme:



2. Experimental section:

2.1

Methyl-(R)-2-(4-((2-(5-chlorothien-2-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02159-1)

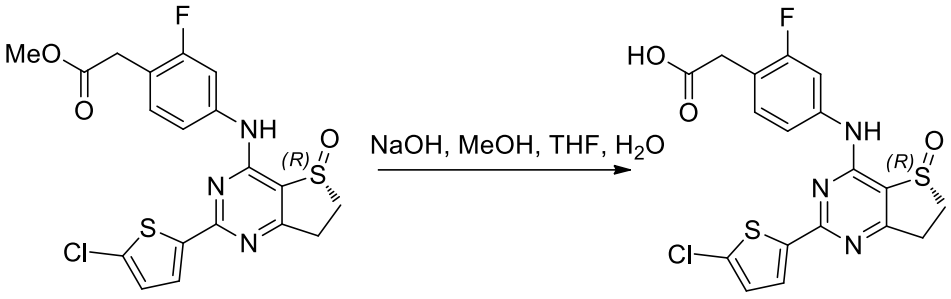


To a solution of (R)-2-(4-((2-chloro-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (70 mg, 0.19 mmol) in 1,4-dioxane (4 mL) were added (5-chlorothiophen-2-yl)boronic acid (30.59 mg, 0.19 mmol), $RuPhosPdG_2$ (13.88 mg, 0.02 mmol), K_3PO_4 (120 mg, 0.57 mmol) and water (0.5 mL) at room temperature. The mixture was stirred at 85°C under argon atmosphere for 4 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH = 0:1 to 1:10, silica gel CS 12 g, 20 mL/min, silica gel, UV 254) to afford a yellow solid product (45 mg, 52.9% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{15}ClFN_3O_3S_2]$ $[M+H]^+$: 452.0; found: 452.2

2.2

(R)-2-(4-((2-(5-chloro-2-thienyl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02159)

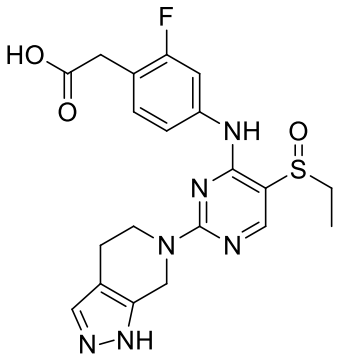


02159-1 **MX02159**

To a solution of (R)-2-(4-((2-(5-chlorothiophen-2-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (40 mg, 0.09 mmol) in MeOH/THF (3 mL, v/v 1:1) was added 2N NaOH aqueous solution at room temperature to adjust the pH to 12. The mixture was stirred at room temperature under nitrogen atmosphere for 3 hours. After the starting material was consumed, the pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (17.06 mg, 44.0% yield).

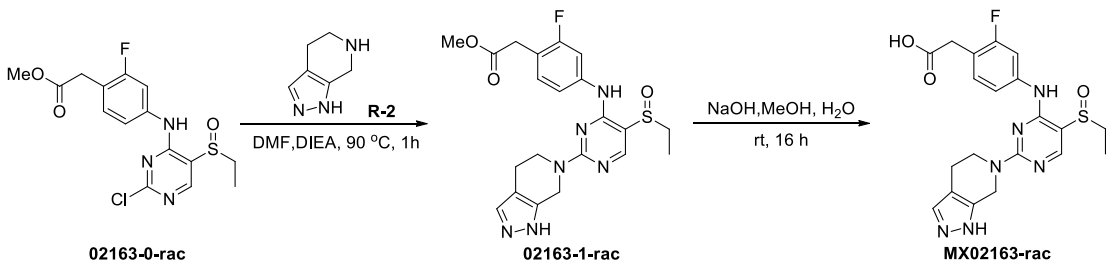
ESI-MS *m/z* calcd for $[C_{18}H_{13}ClFN_3O_3S_2]$ $[M+H]^+$: 438.0; found: 437.7

^{1}H NMR (400 MHz, DMSO-d_6) δ10.02 (br, 1H), 7.75 (d, *J* = 4.0 Hz, 1H), 7.67 (dd, *J* = 12.4, 2.0 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.34 (t, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 4.0 Hz, 1H), 3.77 – 3.68 (m, 1H), 3.57 (s, 2H), 3.47 – 3.40 (m, 1H), 3.34 – 3.28 (m, 1H), 3.16 – 3.11 (m, 1H).



MX02163-rac

1. Synthetic scheme:

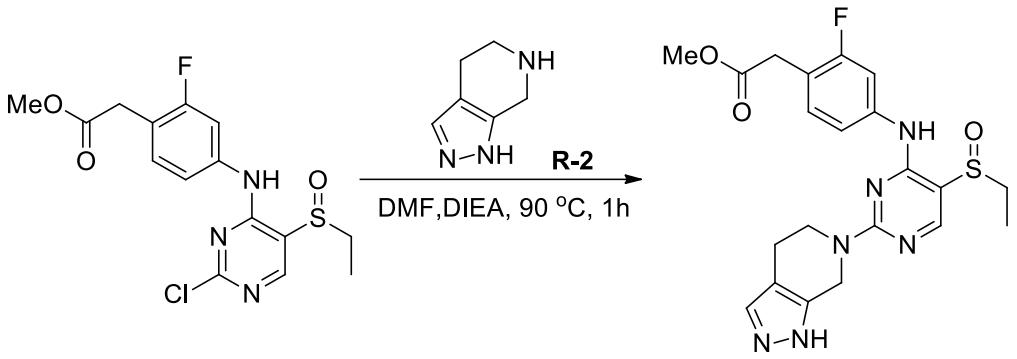


02163-0-rac **02163-1-rac** **MX02163-rac**

2. Experimental section:

2.1

Methyl-2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02163-1-rac)



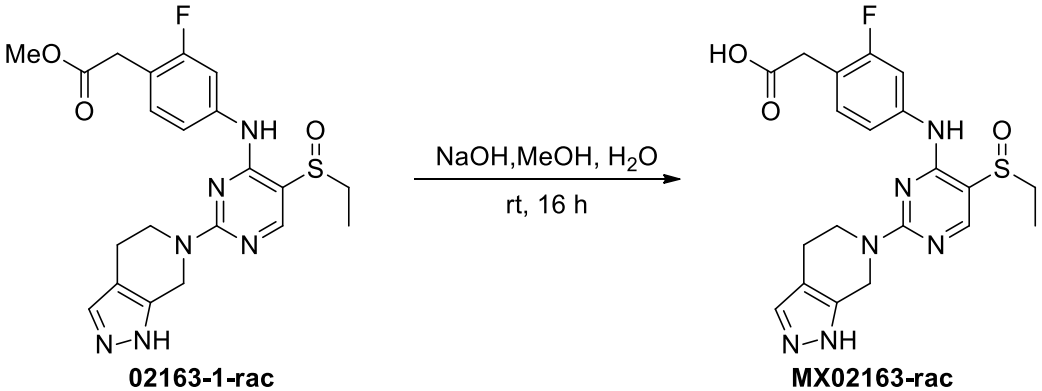
02163-0-rac **02163-1-rac**

To a solution of 2-(4-((2-chloro-5-(ethylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (47 mg, 0.13 mmol) and DIPEA (65 mg, 0.51 mmol) in DMF (3 mL) was added 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine dihydrochloride (29.7 mg, 0.15 mmol) at room temperature. The mixture was stirred at 90°C for 1 hour. The reaction mixture was concentrated under reduced pressure. The crude product was purified by reversed-phase column chromatography (MeCN/H_2O = 0% to 40%, C-18 column, 50 mL/min, UV 214) to afford a yellow solid product (36 mg, 62.11% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{23}FN_6O_3S]$ $[M+H]^+$:459.2; found: 458.8

2.2

2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02163-rac)



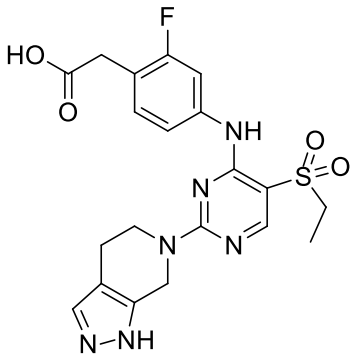
02163-1-rac **MX02163-rac**

To a solution of 2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(ethylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (36 mg, 0.08 mmol) in MeOH (3 mL) was added NaOH (31.4 mg, 0.79 mmol) in water (1 mL) at room

temperature. The mixture was stirred at room temperature for 16 hours. The pH of the solution was adjusted to 6 with AcOH. The solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (23.67 mg, 67.83% yield).

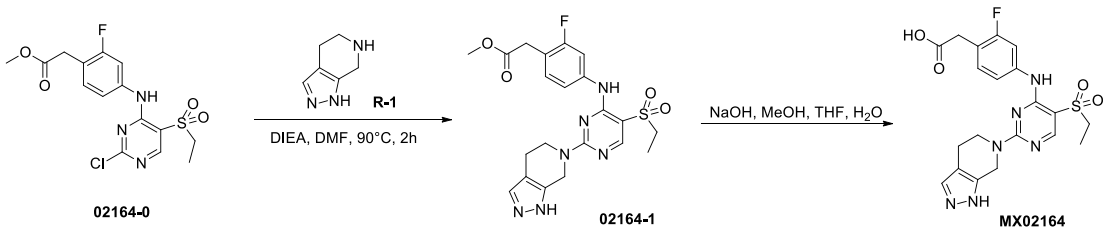
ESI-MS *m/z* calcd for $[C_{20}H_{21}FN_6O_3S]$ $[M+H]^+$:445.1; found: 445.2

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.19 (s, 1H), 7.64 – 7.60 (m, 1H), 7.46 (s, 1H), 7.29 (t, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 4.88 – 4.84 (m, 2H), 4.03 – 3.98 (m, 2H), 3.43 (s, 2H), 3.15 – 3.06 (m, 2H), 2.65 – 2.61 (m, 2H), 1.15 (t, *J* = 7.6 Hz, 3H).



MX02164

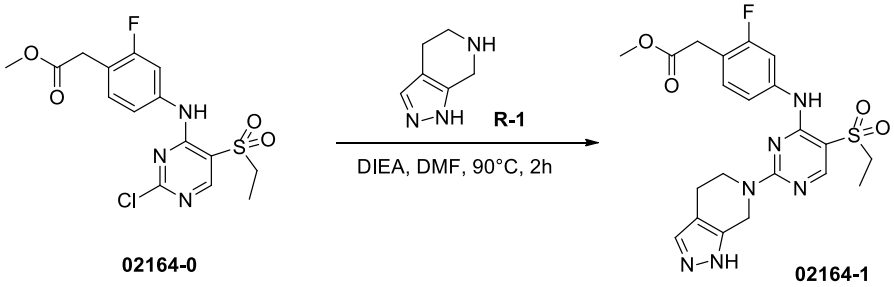
1. Synthetic scheme:



2. Experimental section:

2.1

Methyl-2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02164-1)



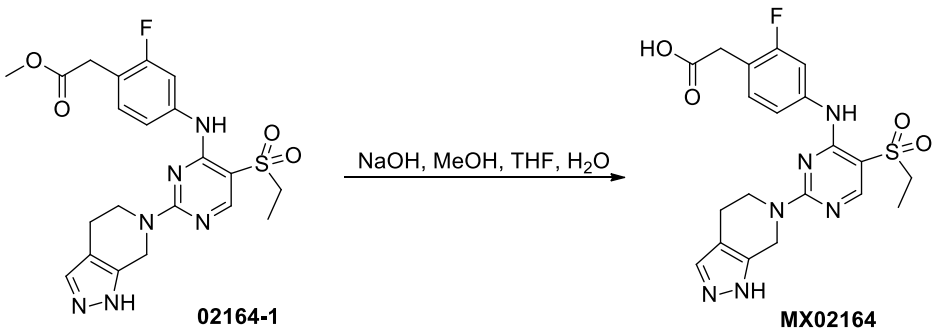
To a solution of 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-

fluorophenyl)acetic acid methyl ester (50 mg, 0.13 mmol) in DMF (2 mL) were added 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (17 mg, 0.14 mmol) and DIEA (50 mg, 0.39 mmol) at 90°C under nitrogen atmosphere. The mixture was stirred at 90°C for 2 hours. After the starting material was consumed, the mixture was cooled and water (10 mL) was added. The mixture was extracted with ethyl acetate (EA, 10 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 1:1, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a white solid product (31 mg, 51% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{23}FN_6O_4S]$ $[M+H]^+$: 475.2; found: 474.6

2.2

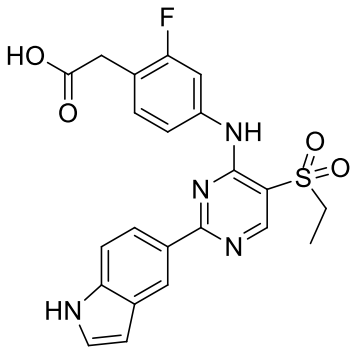
2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (MX02164)



To a solution of 2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (31 mg, 0.06 mmol) in MeOH/THF (2 mL, v/v 1:1) was added 2N NaOH aqueous solution at room temperature. The mixture was stirred at room temperature under nitrogen atmosphere for 3 hours. After the starting material was consumed, the pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (2.07 mg, 7% yield).

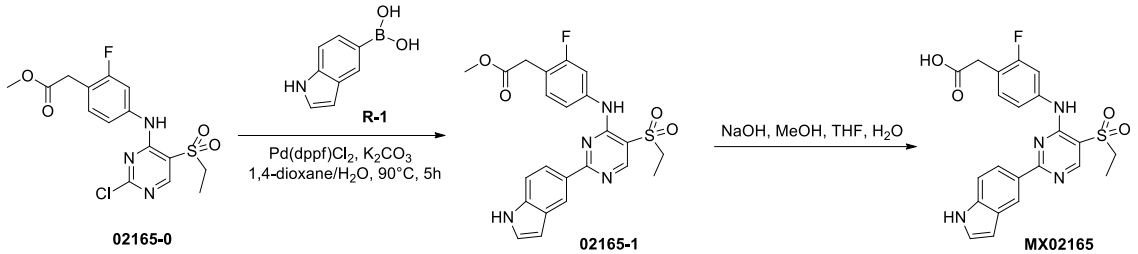
ESI-MS *m/z* calcd for $[C_{20}H_{21}FN_6O_4S]$ $[M+H]^+$: 461.1; found: 461.2

^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 8.39 (s, 1H), 7.65 – 7.55 (m, 1H), 7.48 (s, 1H), 7.35 – 7.27 (m, 2H), 4.96 – 4.84 (m, 2H), 4.09 – 3.96 (m, 2H), 3.52 (s, 2H), 3.34 (q, *J* = 6.8 Hz, 2H), 2.69 – 2.65 (m, 2H), 1.20 (t, *J* = 7.6 Hz, 3H).



MX02165

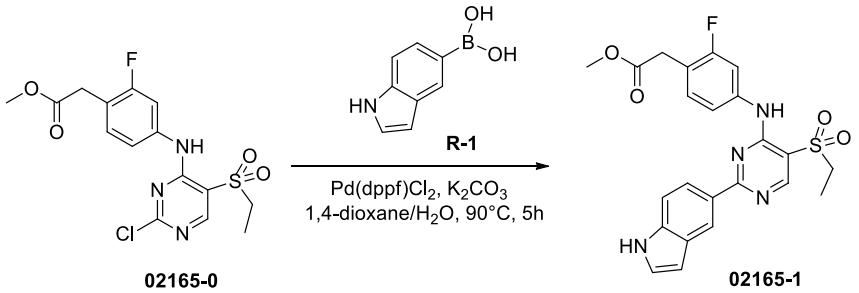
1. Synthetic scheme:



2. Experimental section:

2.1

Methyl-2-(4-((5-(ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02165-1)

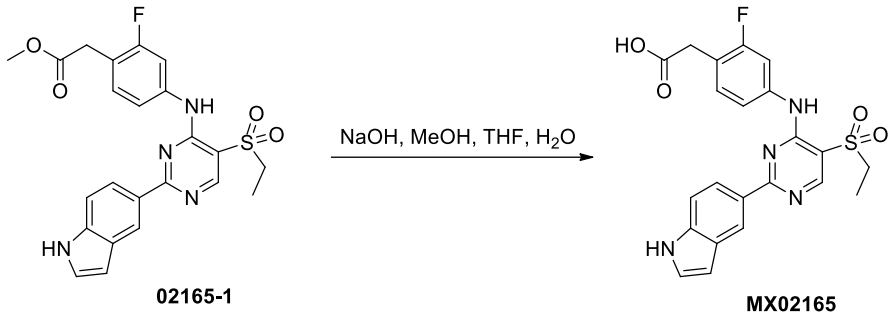


To a solution of 2-(4-(((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (250 mg, 0.64 mmol) and 5-indolylboronic acid (124 mg, 0.77 mmol) in 1,4-dioxane/water (10 mL, v/v 5:1) were added K_2CO_3 (164 mg, 1.28 mmol) and $Pd(dppf)Cl_2$ (43 mg, 0.06 mmol) at 90°C under nitrogen atmosphere. The mixture was stirred at 90°C for 5 hours. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EA = 1:0 to 1:1, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a yellow solid product (244 mg, 81% yield).

ESI-MS *m/z* calcd for $[C_{23}H_{21}FN_4O_4S]$ $[M+H]^+$: 469.1; found: 468.8

2.2

2-(4-((5-(Ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02165)

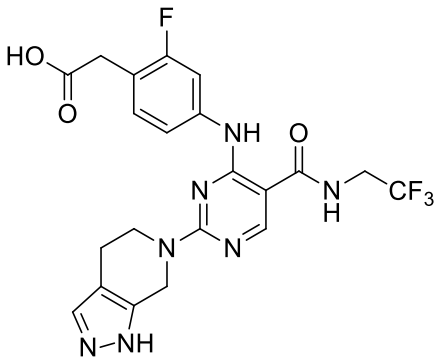


02165-1 MX02165

To a solution of 2-(4-((5-(ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (244 mg, 0.52 mmol) in MeOH/THF (10 mL, v/v 1:1) was added 2N NaOH aqueous solution at room temperature to adjust the pH to 12. The mixture was stirred at room temperature under nitrogen atmosphere for 3 hours. After the starting material was consumed, the pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L HCOOH), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (123 mg, 52% yield).

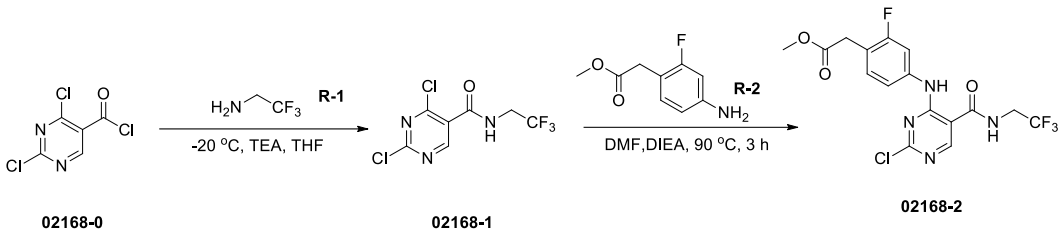
ESI-MS *m/z* calcd for $[C_{22}H_{19}FN_4O_4S]$ $[M+H]^+$: 455.1; found: 455.2

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (brs, 1H), 11.45 (s, 1H), 9.12 (s, 1H), 8.78 (s, 1H), 8.65 (s, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 12.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.44 – 7.39 (m, 3H), 6.57 (s, 1H), 3.64 (s, 2H), 3.53 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

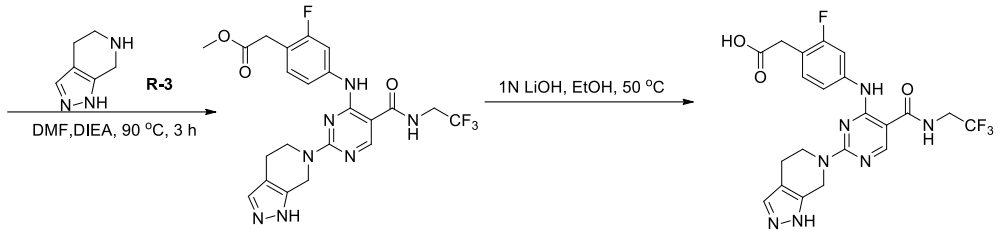


MX02168

1. Synthetic scheme:



02168-0 02168-1 02168-2

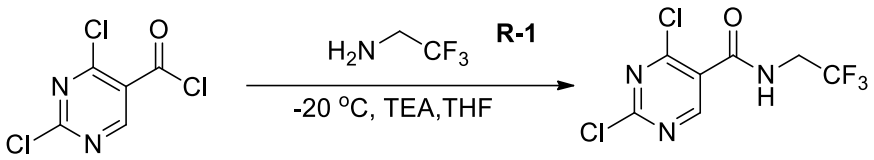


02168-3 MX02168

2. Experimental section:

2.1

2,4-Dichloro-N-(2,2,2-trifluoroethyl)pyrimidine-5-carboxamide(02168-1)



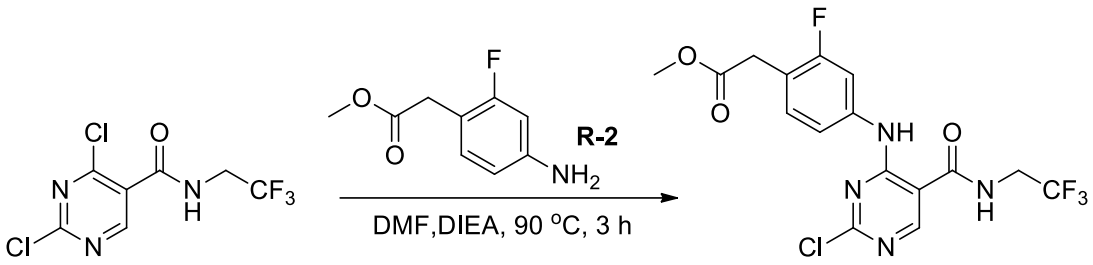
02168-0 **02168-1**

To a solution of 2,4-dichloropyrimidine-5-carbonyl chloride (4.5 g, 21.29 mmol) in anhydrous THF (50 mL) was added dropwise a solution of 2,2,2-trifluoroethylamine (2.11 g, 21.29 mmol) and triethylamine (TEA) (2.15 g, 21.29 mmol) in anhydrous THF (25 mL) at -20°C. The mixture was stirred at -20°C for 2 hours. After the temperature reached room temperature, the mixture was stirred for an additional 10 minutes. The precipitate was filtered off, and the filtrate was evaporated to afford the crude product. The crude product was purified by column chromatography (EA/hexane = 0:1 to 1:2, silica gel CS 40 g, 50 mL/min, silica gel, UV 254) to afford a white solid product (3.7 g, 63.4% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ9.47 (t, J = 6.0 Hz, 1H),8.93 (s, 1H), 4.21 – 4.12 (m, 2H).

2.2

Methyl-2-(4-((2-chloro-5-((2,2,2-trifluoroethyl)aminocarbonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02168-2)



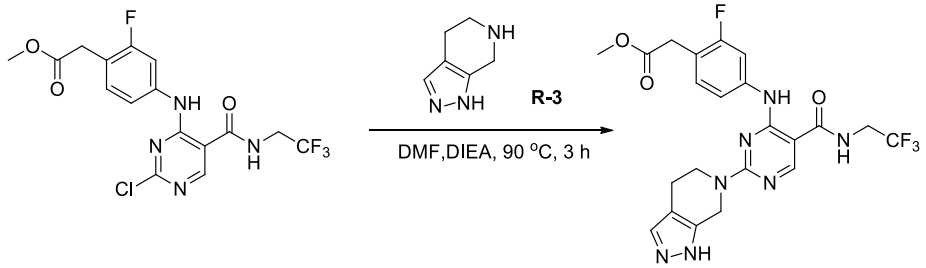
02168-1 02168-2

To a solution of 2,4-dichloro-N-(2,2,2-trifluoroethyl)pyrimidine-5-carboxamide (1.5 g, 5.474 mmol) and DIPEA (1.41 g, 10.948 mmol) in DMF (20 mL) was added 2-(4-amino-2-fluorophenyl)acetic acid methyl ester (1 g, 5.47 mmol) at room temperature. The mixture was stirred at 90°C for 3 hours. The reaction mixture was concentrated under reduced pressure. Water (10 mL) was added, and the mixture was extracted with DCM (30 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0:1 to 1:1, silica gel CS 40 g, 40 mL/min, silica gel, UV 254) to afford a yellow solid product (1.9 g, 82.6% yield).

ESI-MS m/z calcd for $[C_{16}H_{13}ClF_4N_4O_3]$ $[M+H]^+$:421.2; found:420.8

2.3

2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-((2,2,2-trifluoroethyl)aminocarbonyl)pyrimidin-4-yl)amino)-2-fluorophenyl) Methyl 2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]py(02168-3)



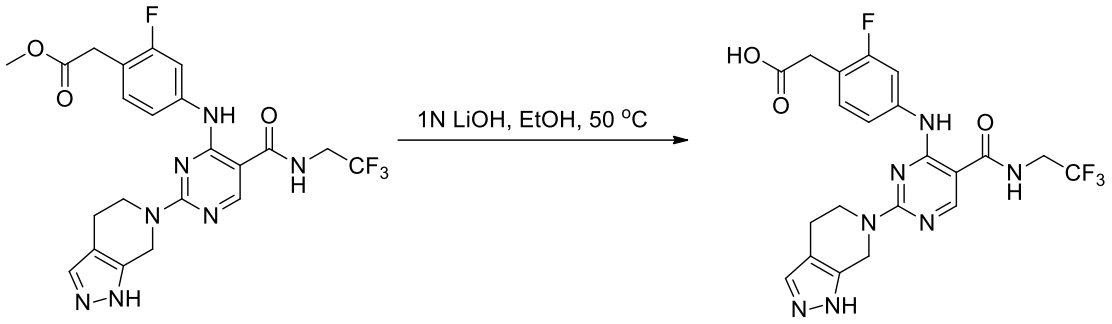
02168-2 02168-3

To a solution of 2-(4-((2-chloro-5-((2,2,2-trifluoroethyl)carbamoyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (50 mg, 0.119 mmol) and DIPEA (46.1 mg, 0.356 mmol) in DMF (2 mL) was added 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (17.6 mg, 0.143 mmol) at 90°C. The mixture was stirred at 90°C for 1 hour. The solvent was removed under reduced pressure. Water (10 mL) was added, and the mixture was extracted with ethyl acetate (EA, 10 mL) twice. The combined organic layers were washed with saturated saturated

brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product (brown) was used directly for the next step.

2.4

2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-((2,2,2-trifluoroethyl)aminocarbonyl)pyrimidin-4-yl)amino)-2-fluorophenyl) Acetic acid (02438-4)

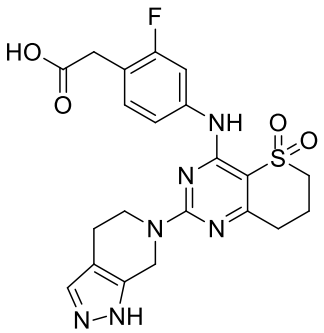


02168-3 MX02168

To a solution of 2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-((2,2,2-trifluoroethyl)carbamoyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (crude, 0.110 mmol) in EtOH (2 mL) was added 1N NaOH (0.6 mL, 0.6 mmol) at room temperature. The mixture was stirred at 50°C under nitrogen atmosphere for 1 hour. After the starting material was consumed, the pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (12.93 mg, 22% yield).

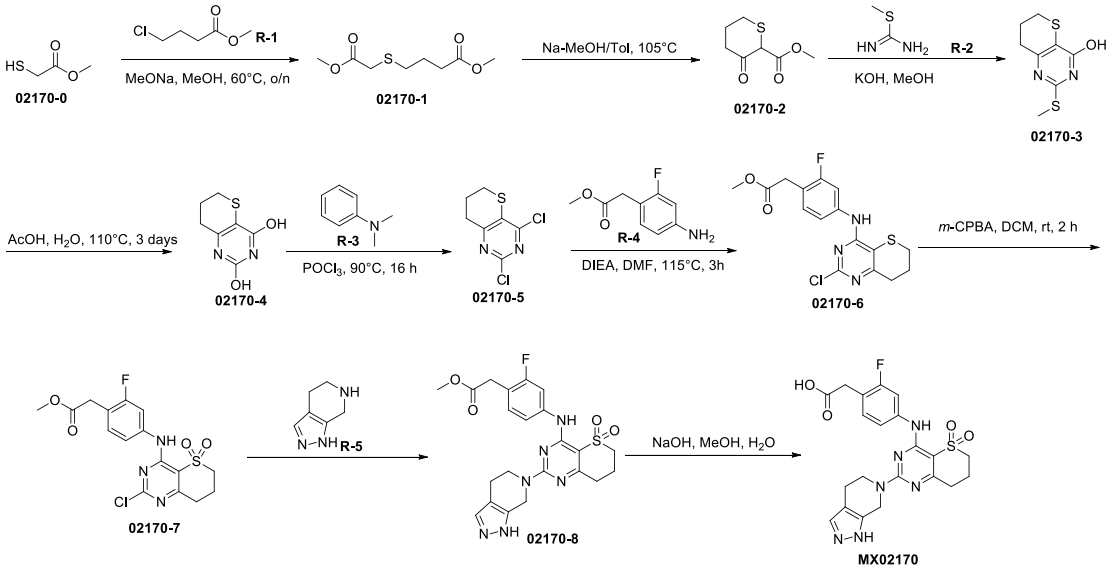
ESI-MS *m/z* calcd for $[C_{21}H_{19}F_4N_7O_3]$ $[M+H]^+$:494.2; found: 494.1

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (br, 1H), 11.22 (s, 1H), 9.04 (t, *J* = 6.0 Hz, 1H), 8.74 (s, 1H), 7.77 (d, *J* = 11.2 Hz, 1H), 7.47 (s, 1H), 7.33 – 7.25 (m, 2H), 4.92 – 4.88 (m, 2H), 4.12 – 4.05 (m, 4H), 3.58 (s, 2H), 2.67 – 2.66 (m, 2H).



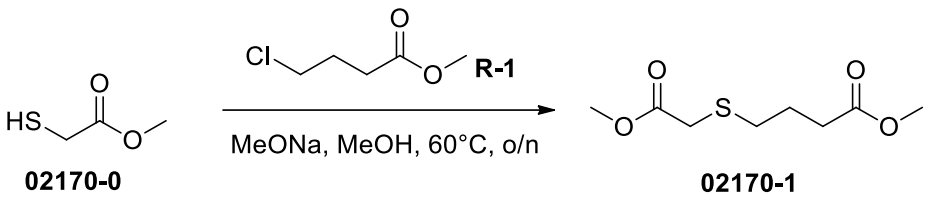
MX02170

1. Synthetic scheme:



2. Experimental section:

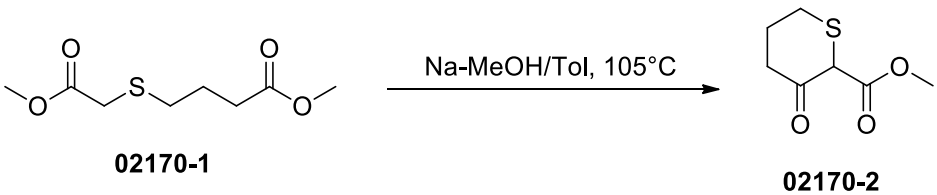
2.1 Methyl 4-((2-methoxy-2-oxoethyl)thio)butanoate(02170-1)



To a solution of sodium methoxide (1.62 g, 29.96 mmol) in MeOH (30 mL) was added methyl 2-mercaptoacetate (2.65 g, 24.97 mmol) at room temperature. The mixture was stirred at room temperature for 0.5 hours. Then NaI (37.4 mg, 0.25 mmol) and methyl 4-chlorobutyrate (4.09 g, 29.96 mmol) were added at 65°C. The mixture was stirred at 65°C for 20 hours, cooled to room temperature, and concentrated under reduced pressure. The crude product was dissolved in DCM (100 mL), washed with water (20 mL) and saturated saturated brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/hexane = 0:1 to 22:100, silica gel CS 80 g, 50 mL/min, silica gel, UV 254) to afford a yellow oily product (2.8 g, 54.37% yield).

ESI-MS *m/z* calcd for $[C_8H_{14}O_4S]$ $[M+H]^+$:207.1; found: 207.2

2.2 Methyl 3-oxo-2H-thien-2-carboxylate(02170-2)

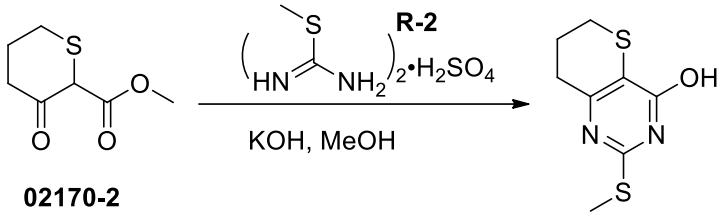


To a mixture of sodium (1.09 g, 47.51 mmol) in toluene (200 mL) was added MeOH (20 mL) at 100°C. The mixture was stirred at 100°C for 3 hours. MeOH was removed under

reduced pressure. To the mixture at 100°C, 4-((2-methoxy-2-oxoethyl)sulfanyl)butanoic acid methyl ester (2.8 g, 13.58 mmol) in toluene (10 mL) was added. The mixture was stirred at 110°C for 1 hour, cooled to room temperature, and poured into a mixture of concentrated HCl (10 mL) and ice (100 g). The mixture was extracted EA (100 mL) twice. The combined organic layers were washed with saturated saturated brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 25:100, silica gel CS 80 g, 50 mL/min, silica gel, UV 254) to afford a yellow oily product (1.5 g, 63.42% yield).

ESI-MS *m/z* calcd for $[C_7H_{10}O_3S]$ $[M+H]^+$:175.0; found: 175.4

2.3 2-(Methylthio)-7,8-dihydro-6H-thieno[3,2-d]pyrimidin-4-ol(02170-3)

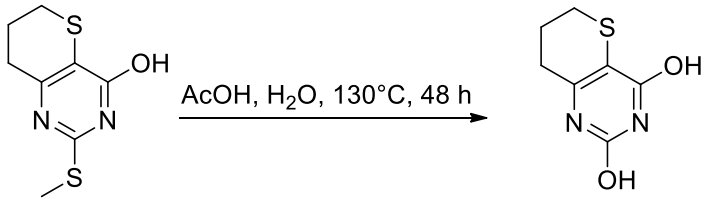


02170-2 **02170-3**

To a solution of KOH (1.01 g, 18.08 mmol) in MeOH (40 mL) were added methyl 3-oxotetrahydro-2H-thiopyran-2-carboxylate (2.1 g, 12.05 mmol) and bis(S-methylthio)ammonium sulfate (1.68 g, 6.03 mmol) at room temperature. The mixture was stirred at room temperature for 20 hours. The mixture was poured into ice water and AcOH (3 mL) was added. The solid was filtered, washed with water and MTBE, to afford a white solid product (1.8 g, 69.68% yield).

ESI-MS *m/z* calcd for $[C_8H_{10}N_2OS_2]$ $[M+H]^+$:215.0; found: 215.2

2. 4 7,8-Dihydro-6H-thieno[3,2-d]pyrimidine-2,4-diol(02170-4)

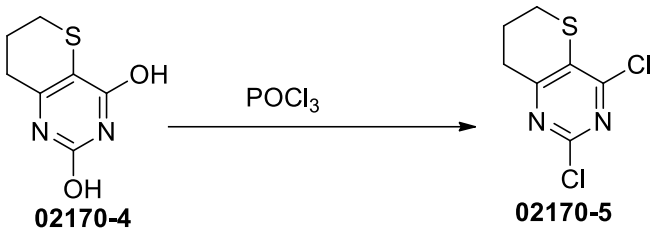


02170-3 **02170-4**

To a suspension of 2-(methylthio)-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-ol (1.8 g, 8.40 mmol) in water (20 mL) was added AcOH (40 mL) at 130°C. The mixture was stirred at 130°C for 48 hours. After cooling to room temperature, the mixture was concentrated under vacuum. The crude product was washed with EtOH to afford a white solid product (1.1 g, 71.09% yield).

ESI-MS *m/z* calcd for $[C_7H_8N_2O_2S]$ $[M+H]^+$:185.0; found: 184.9

2.5 2,4-Dichloro-7,8-dihydro-6H-thieno[3,2-d]pyrimidine(02170-5)



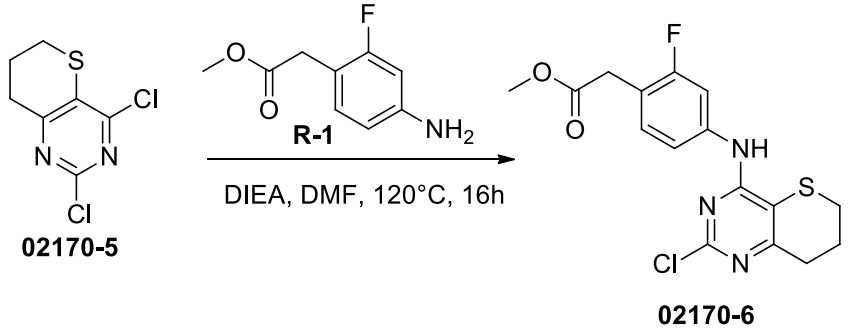
02170-4 02170-5

To a suspension of 7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine-2,4-diol (1.1 g, 5.97 mmol) in $POCl_3$ (15 mL) was added N,N-dimethylaniline (145 mg, 1.19 mmol) at room temperature. The mixture was stirred at 90°C for 16 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure. The crude product was dissolved in DCM (100 mL) and washed twice with saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 30:70, silica gel CS 40 g, 50 mL/min, silica gel, UV 254) to afford a yellow solid product (1.0 g, 75.74% yield).

ESI-MS *m/z* calcd for $[C_7H_6Cl_2N_2S]$ $[M+H]^+$:221.0; found: 221.0

2.6

Methyl-2-(4-((2-chloro-7,8-dihydro-6H-thieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02170-6)



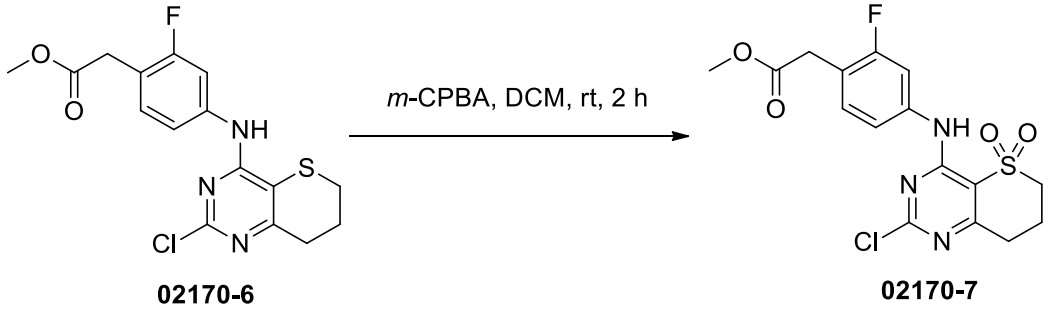
02170-5 02170-6

To a solution of 2,4-dichloro-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (500 mg, 2.26 mmol) and 2-(4-amino-2-fluorophenyl)acetic acid methyl ester (621 mg, 3.39 mmol) in DMF (10 mL) was added DIEA (1.17 g, 9.05 mmol) at 120°C. The mixture was stirred at 120°C for 16 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0:1 to 25:75, silica gel CS 20 g, 25 mL/min, silica gel, UV 254) to afford a yellow solid product (301 mg, 36.19% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{15}ClFN_3O_2S]$ $[M+H]^+$:368.1; found:367.9

2.7

Methyl-2-(4-(((2-chloro-5,5-dioxo-7,8-dihydro-6H-thieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02170-7)



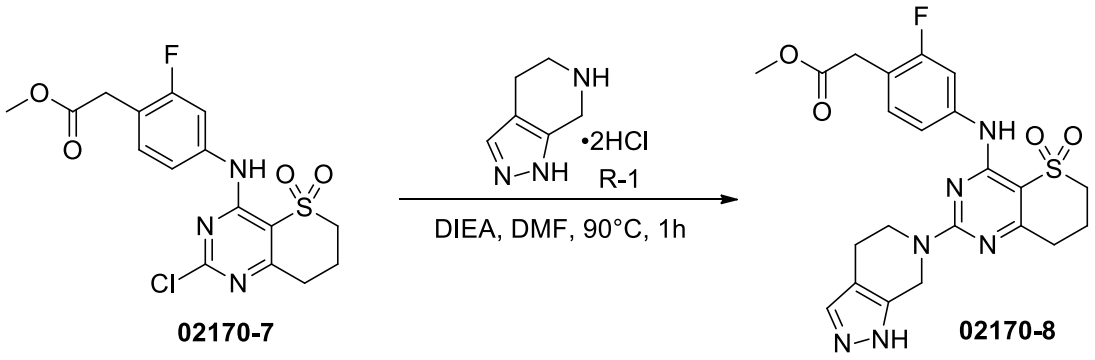
02170-6 02170-7

To a solution of 2-(4-((2-chloro-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (120 mg, 0.33 mmol) in DCM (10 mL) was added m-CPBA (85%, 225 mg, 0.98 mmol) at room temperature. The mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with DCM (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/DCM = 0:1 to 30:70, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a white solid product (107 mg, 82.03% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{15}ClFN_3O_4S]$ $[M+H]^+$:400.1; found: 400.0

2.8

2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5, 5-dioxo-7,8-dihydro-6H-thieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (02170-8)



02170-7 02170-8

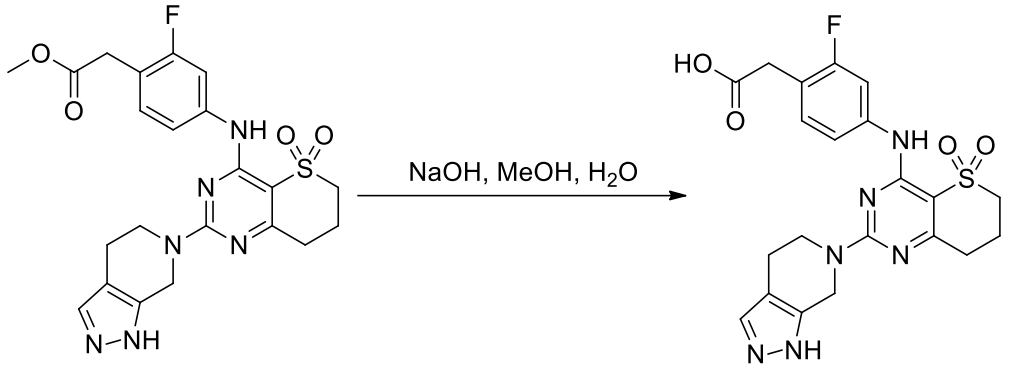
To a solution of 2-(4-((2-chloro-5,5-dioxo-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (40 mg, 0.10 mmol) and 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine dihydrochloride (23.5 mg, 0.12 mmol) in DMF (3 mL) was added DIPEA (77.6 mg, 0.60 mmol) at 90°C under nitrogen atmosphere. The mixture was stirred at 90°C for 1 hour. After cooling, the mixture was concentrated under reduced pressure.

The crude product was purified by reversed-phase column chromatography (MeCN/H_2O = 0:40%, C-18 column, 40 g, 50 mL/min, UV 254) to afford a white solid product (40 mg, 82.18% yield).

ESI-MS *m/z* calcd for $[C_{27}H_{27}FN_6O_5S]$ $[M+H]^+$: 487.2; found: 487.0

2.9

2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5, 5-dioxo-7,8-dihydro-6H-thieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02170)

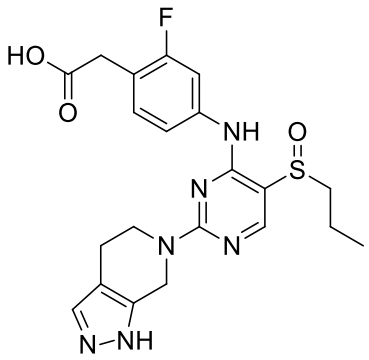


02170-8 **MX02170**

To a solution of 2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5,5-dioxo-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (40 mg, 0.082 mmol) in MeOH (3 mL) was added NaOH (16.4 mg, 0.41 mmol) in water (1 mL) at room temperature. The mixture was stirred at room temperature for 2 hours. The pH of the solution was adjusted to 6 with AcOH. The mixture was filtered, and the filtrate was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (33.23 mg, 85.54% yield).

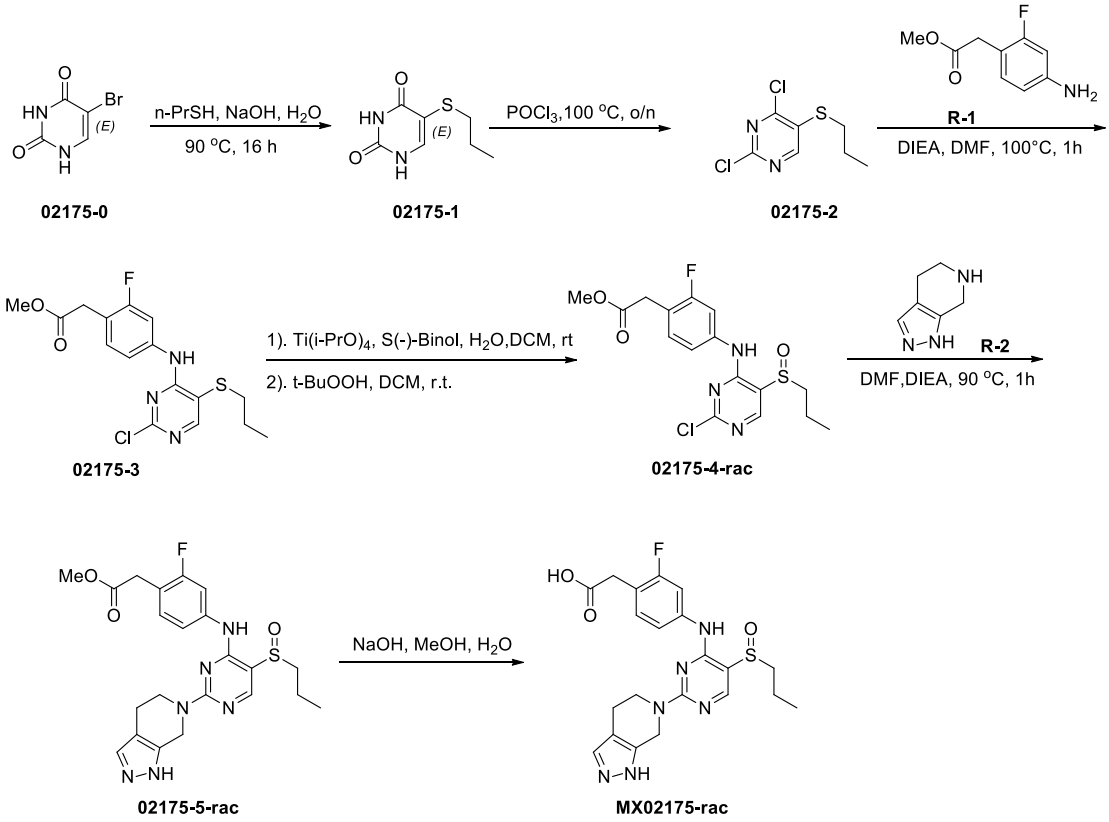
ESI-MS *m/z* calcd for $[C_{21}H_{21}FN_6O_4S]$ $[M+H]^+$:473.1; found: 473.0

^1H NMR (400 MHz, Methanol-d_4) δ 7.54 – 7.52 (m, 1H), 7.40 (s, 1H), 7.30 (t, J = 8.4 Hz, 1H), 7.19 – 7.17 (m, 1H), 4.91 – 4.90 (m, 2H), 4.07 (s, 2H), 3.55 (s, 2H), 3.47 – 3.44 (m, 2H), 2.88 (t, J = 6.4 Hz, 2H), 2.71 – 2.68 (m, 2H), 2.44 – 2.38 (m, 2H).



MX02175-rac

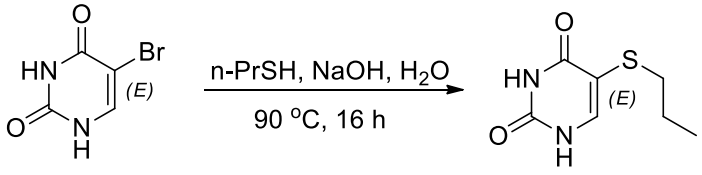
1. Synthetic scheme:



02175-0 **02175-1** **02175-2** **02175-3** **02175-4-rac** **02175-5-rac** **MX02175-rac**

2. Experimental section:

2.1 5-(Propylthio)pyrimidine-2,4(1H,3H)-dione(02175-1)



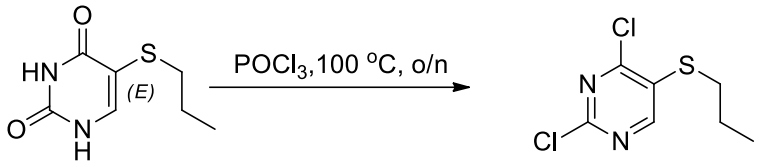
02175-0 **02175-1**

To a suspension of 5-bromo-2,4(1H,3H)-pyrimidinedione (3.20 g, 16.76 mmol) in water (60 mL) was added NaOH (1.34 g, 33.51 mmol) and propane-1-thiol (2.55 g, 33.51 mmol) at room temperature. The mixture was stirred at 90°C for 16 hours. After cooling to room

temperature, the pH of the solution was adjusted to 7 with concentrated HCl. The mixture was filtered, and the solid was washed with water (10 mL), MTBE (50 mL), MeCN (20 mL) and MTBE (50 mL) to afford a white solid product (1.0 g, crude).

ESI-MS *m/z* calcd for $[C_7H_{10}N_2O_2S]$ $[M+H]^+$:187.1; found: 187.2

2.2 2,4-Dichloro-5-(propylthio)pyrimidine(02175-2)



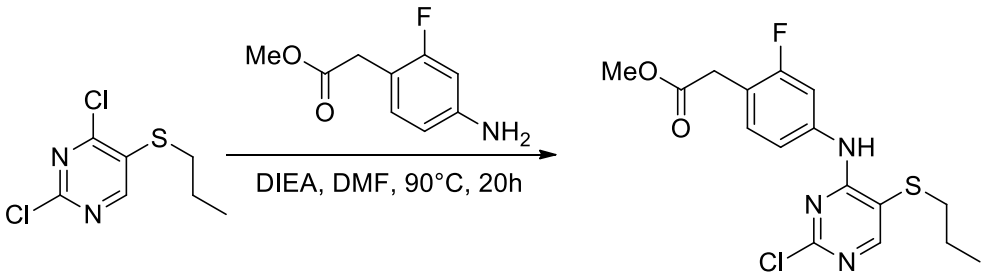
02175-1 **02175-2**

A suspension of 5-(propylthio)pyrimidine-2,4(1H,3H)-dione (crude product from the previous step, 1 g) in $POCl_3$ (15 mL) was stirred at 100°C overnight, cooled to room temperature, and concentrated under reduced pressure. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the mixture was extracted with ethyl acetate (EA, 20 mL) twice. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 30:70, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a white solid product (202 mg, 5.40% yield over two steps).

ESI-MS *m/z* calcd for $[C_7H_8Cl_2N_2S]$ $[M+H]^+$:223.0; found: 222.9

2.3

Methyl-2-(4-((2-chloro-5-(propylthio)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02175-3)



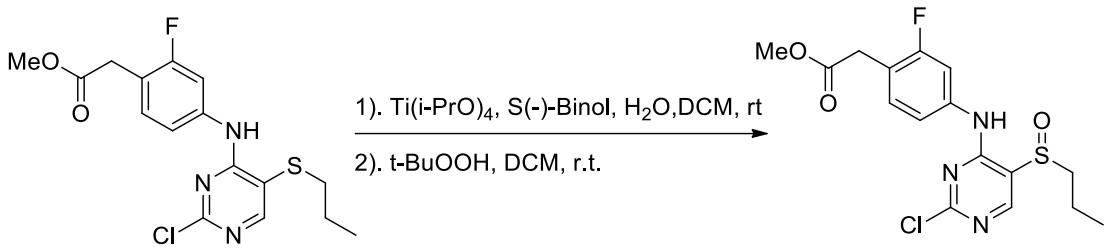
02175-2 **02175-3**

To a solution of 2,4-dichloro-5-(propylthio)pyrimidine (202 mg, 0.91 mmol) and 2-(4-amino-2-fluorophenyl)acetic acid methyl ester (199 mg, 1.09 mmol) in DMF (10 mL) was added DIEA (585 mg, 4.53 mmol) at 90°C. The mixture was stirred at 90°C for 20 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 25:75, silica gel CS 20 g, 25 mL/min, silica gel, UV 254) to afford a yellow solid product (171 mg, 51.07% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{17}ClFN_3O_2S]$ $[M+H]^+$:370.1; found:369.8

2. 4

Methyl-2-(4-((2-chloro-5-(propylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02175-4-rac)



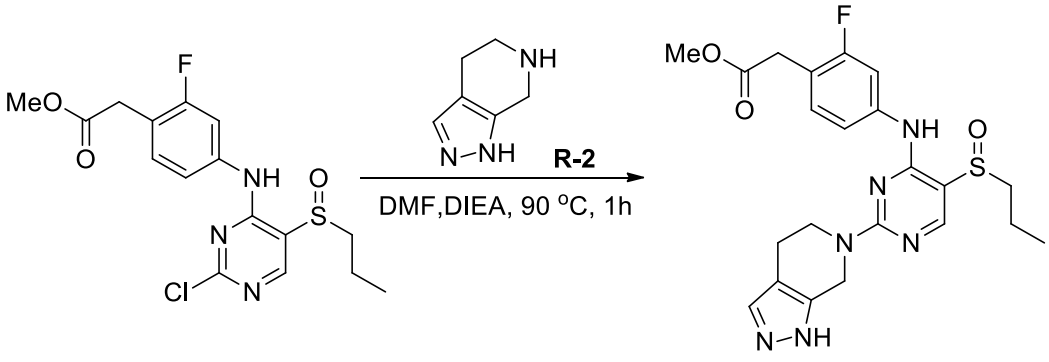
02175-3 **02175-4-rac**

To a solution of 2-(4-((2-chloro-5-(propylthio)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (50 mg, 0.14 mmol) and (S)-(-)-1,1'-binaphthol (19.2 mg, 0.068 mmol) in DCM (5 mL) were added titanium tetraisopropoxide (19.4 mg, 0.068 mmol) and water (4.9 mg, 0.27 mmol) at room temperature. The mixture was stirred at room temperature overnight. Then 70% tert-butyl hydroperoxide aqueous solution (69.6 mg, 0.54 mmol) was added all at once. The mixture was stirred at room temperature for another 2 hours. The reaction mixture was concentrated under reduced pressure. Saturated aqueous $NaHCO_3$ solution (40 mL) was added and the mixture was extracted with EA (40 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (MeOH/DCM = 0:1 to 5:95, silica gel CS 20 g, 25 mL/min, silica gel, UV 254) to afford a white solid product (33 mg, 63.26% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{17}ClFN_3O_3S]$ $[M+H]^+$:386.1; found: 386.0

2.5

Methyl-2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(propylsulphonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02175-4-rac)



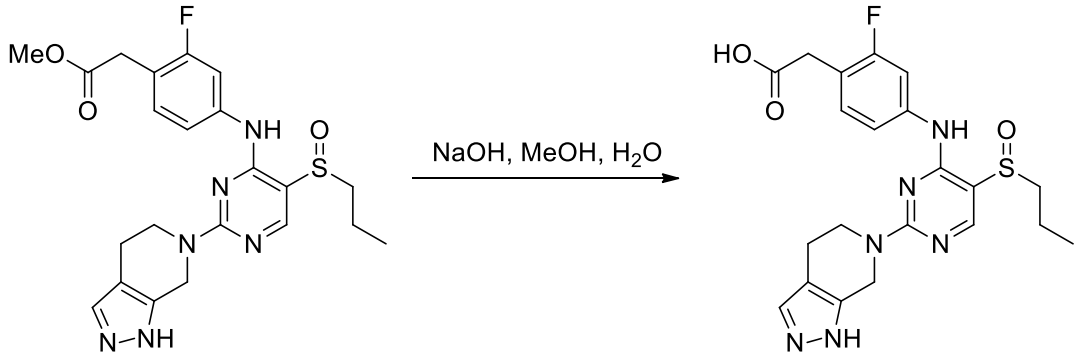
02175-4-rac **02175-5-rac**

To a solution of 2-(4-((2-chloro-5-(propylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (45 mg, 0.12 mmol) and DIPEA (60.3 mg, 0.47 mmol) in DMF (3 mL) was added 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine dihydrochloride (27.4 mg, 0.14 mmol) at 90°C. The mixture was stirred at 90°C for 1 hour. The reaction mixture was concentrated under reduced pressure. Saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with EA (20 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH/DCM = 0:1 to 4:96, silica gel CS 4 g, 12 mL/min, silica gel, UV 254) to afford a yellow oily product (32 mg, 58.06% yield).

ESI-MS *m/z* calcd for $[C_{22}H_{25}FN_6O_3S]$ $[M+H]^+$:473.2; found: 473.2

2.6

2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(propylsulphonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02175-rac)

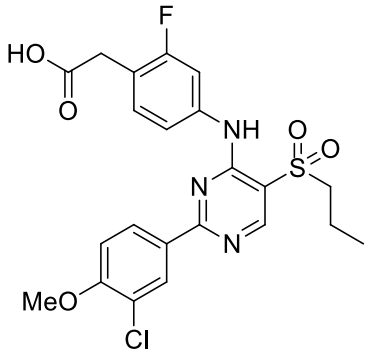


02175-5-rac **MX02175-rac**

To a solution of 2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(propylsulfinyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (32 mg, 0.068 mmol) in MeOH (3 mL) was added NaOH (27 mg, 0.68 mmol) in water (1 mL) at room temperature. The mixture was stirred at room temperature for 2 hours. The pH of the solution was adjusted to 6 with AcOH. The mixture was filtered, and the filtrate was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (25 mg, 80.52% yield).

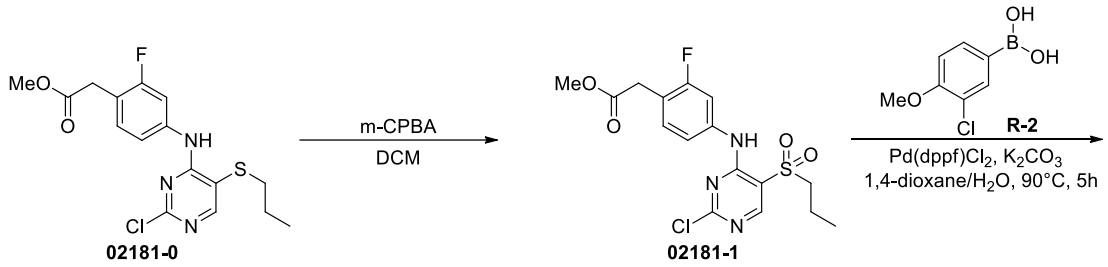
ESI-MS *m/z* calcd for $[C_{21}H_{23}FN_6O_3S]$ $[M+H]^+$:459.2; found: 459.2

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 – 9.66 (m, 1H), 8.19 (s, 1H), 7.64 – 7.61 (m, 1H), 7.46 – 7.44 (m, 1H), 7.29 (t, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 4.91 – 4.85 (m, 2H), 4.07 – 3.96 (m, 2H), 3.57 – 3.56 (m, 2H), 3.25 – 3.13 (m, 1H), 3.04 - 2.96 (m, 1H), 2.74 – 2.65 (m, 2H), 1.66 -1.56 (m, 2H), 0.99 (t, *J* = 8.8 Hz, 3H).



MX02180

1. Synthetic scheme:

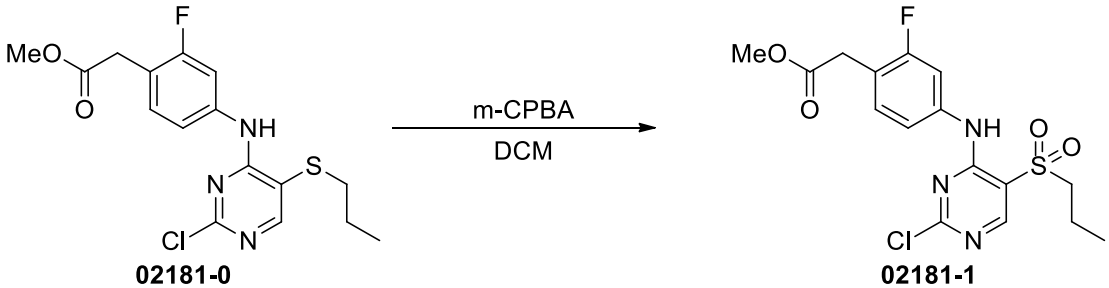


02181-0 **02181-1** **02180-2** **MX02180**

2. Experimental section:

2.1

Methyl-2-(4-((2-chloro-5-(propylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02181-1)



02181-0 **02181-1**

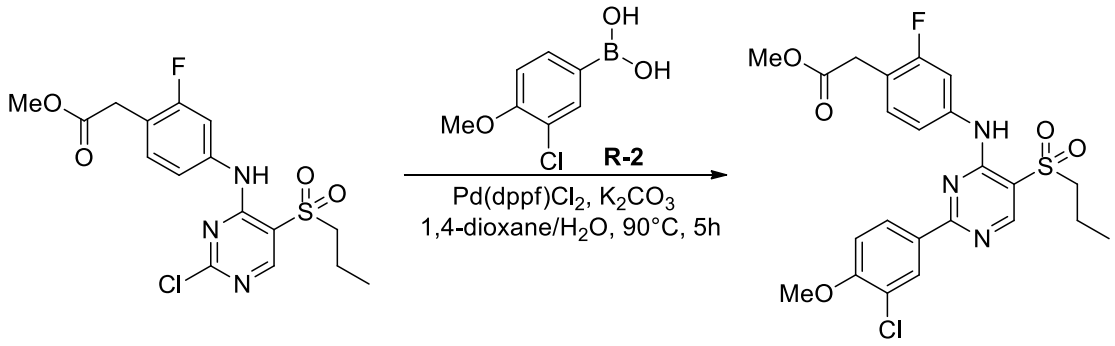
To a solution of 2-(4-((2-chloro-5-(propylthio)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (60 mg, 0.16 mmol) in DCM (10 mL) was added m-

CPBA (85%, 132 mg, 0.65 mmol) at room temperature. The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with DCM (20 mL) twice. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0:1 to 45:55, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a white solid product (44 mg, 67.49% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{17}ClFN_3O_4S]$ $[M+H]^+$:402.1; found: 402.2

2.2

Methyl-2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(propylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02180-2)

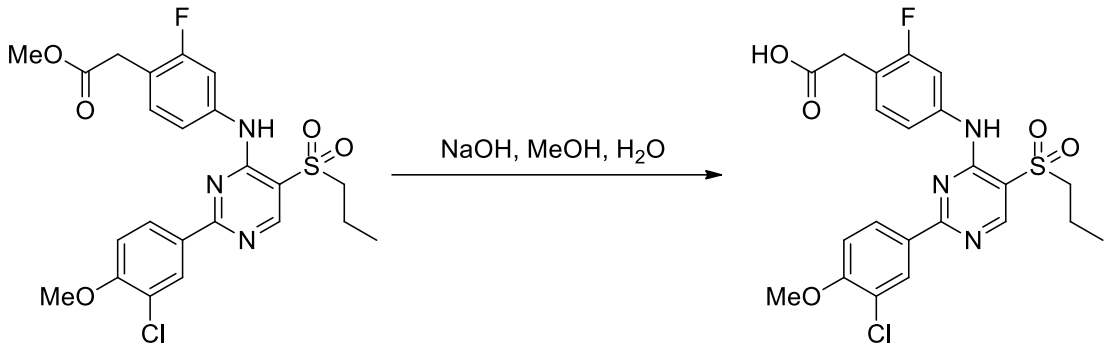


To a solution of 2-(4-((2-chloro-5-(propylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (44 mg, 0.11 mmol) in 1,4-dioxane/water (5 mL, v/v 4:1) were added (3-chloro-4-methoxyphenyl)boronic acid (28.6 mg, 0.15 mmol), K_2CO_3 (60.5 mg, 0.44 mmol), and $Pd(dppf)Cl_2$ (8.9 mg, 0.01 mmol) at 90°C under nitrogen atmosphere. The mixture was stirred at 90°C for 5 hours. After the starting material was consumed, the reaction mixture was quenched with water and extracted with EA(20 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 50:50, silica gel CS 4 g, 12 mL/min, silica gel, UV 254) to afford a yellow solid product (31 mg, 55.74% yield).

ESI-MS *m/z* calcd for $[C_{23}H_{23}ClFN_3O_5S]$ $[M+H]^+$:508.1; found: 508.2

2.3

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5-(propylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02180)

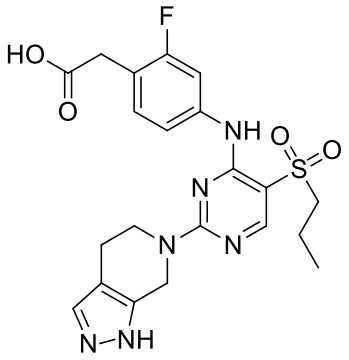


02180-2 **MX02180**

To a solution of 2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(propylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (31 mg, 0.061 mmol) in MeOH (3 mL) was added NaOH (12.2 mg, 0.31 mmol) in water (1 mL) at room temperature. The mixture was stirred at room temperature for 2 hours. The pH of the solution was adjusted to 6 with AcOH. The mixture was filtered. The filtrate was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (3.4 mg, 10.45% yield).

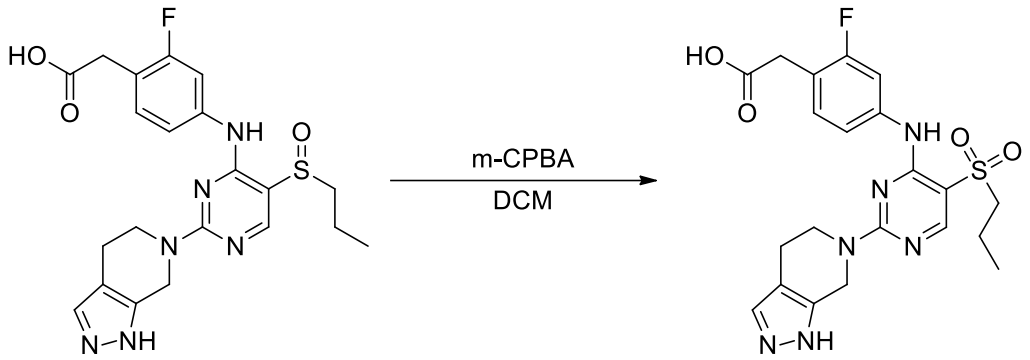
ESI-MS *m/z* calcd for $[C_{22}H_{21}ClFN_3O_5S]$ $[M+H]^+$:494.1; found: 493.8

^1H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.30 – 8.29 (m, 1H), 8.27 – 8.24 (m, 1H), 7.71 – 7.68 (m, 1H), 7.38 – 7.34 (m, 3H), 3.95 (s, 3H), 3.60 (s, 2H), 3.54 – 3.50 (m,2H), 1.76 – 1.70 (m, 2H), 0.98 (t, *J* =7.6 Hz, 3H).



MX02181

1. Synthetic scheme:

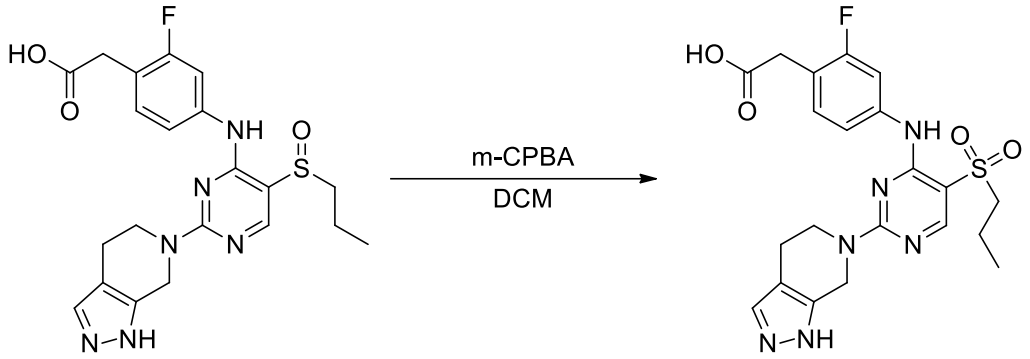


MX02175-rac **MX02181**

2. Experimental section:

2.1

2-(4-((2-(4,5-Dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(propylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02181)

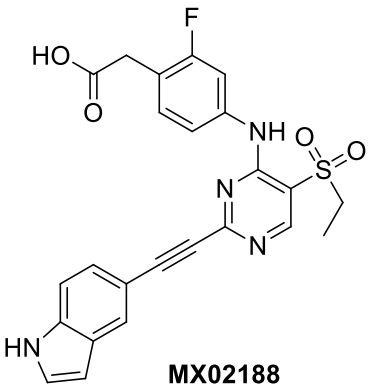


MX02175-rac **MX02181**

To a solution of 2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-(propylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (32 mg, 0.068 mmol) in DCM (3 mL) was added *m*-CPBA (85%, 13.3 mg, 0.065 mmol) at room temperature. The mixture was stirred at room temperature for 16 hours. Water (20 mL) was added, and the mixture was extracted with DCM (20 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a white solid product (13.67 mg, 66.05% yield).

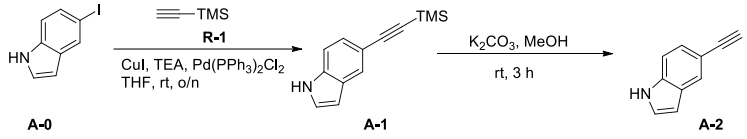
ESI-MS *m/z* calcd for $[C_{21}H_{23}FN_6O_4S]$ $[M+H]^+$:475.2; found: 475.0

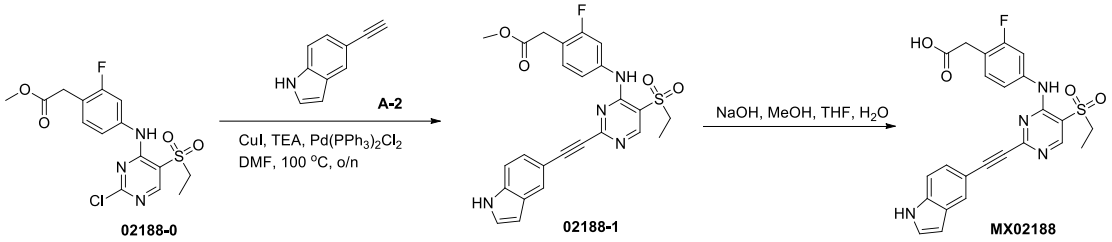
^1H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.62 – 7.56 (m, 1H), 7.47 (s, 1H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 4.95 – 4.82 (m, 2H), 4.09 – 3.98 (m, 2H), 3.48 (s, 2H), 3.36 – 3.32 (m, 2H), 2.67 – 2.63 (m, 2H), 1.68 – 1.63 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H).



MX02188

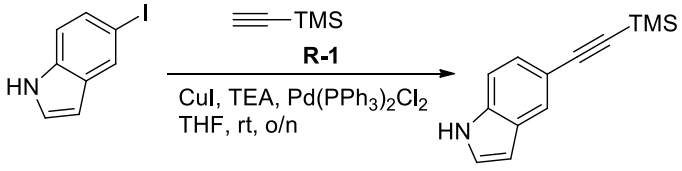
1. Synthetic scheme:





2. Experimental section:

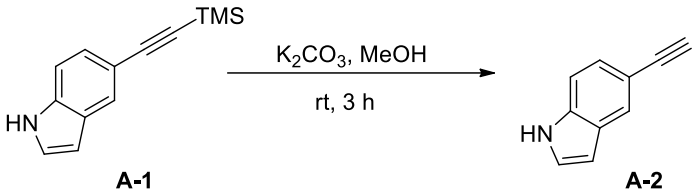
2.1 5-((Trimethylsilyl)ethynyl)-1H-indole(A-1)



To a solution of 5-iodo-1H-indole (1 g, 4.11 mmol) in THF (10 mL) were added trimethylsilylacetylene (444 mg, 4.53 mmol), CuI (78 mg, 0.41 mmol), TEA (5 mL) and $Pd(PPh_3)_2Cl_2$ (84 mg, 0.12 mmol) at room temperature. The mixture was stirred under nitrogen atmosphere overnight. After the starting material was consumed, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 1:10, silica gel CS 40 g, 40 mL/min, silica gel, UV 254) to afford a brown solid product (810 mg, 93% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{15}NSi]$ $[M+H]^+$: 214.1; found: 214.3

2.2 5-Ethynyl-1H-indole(A-2)



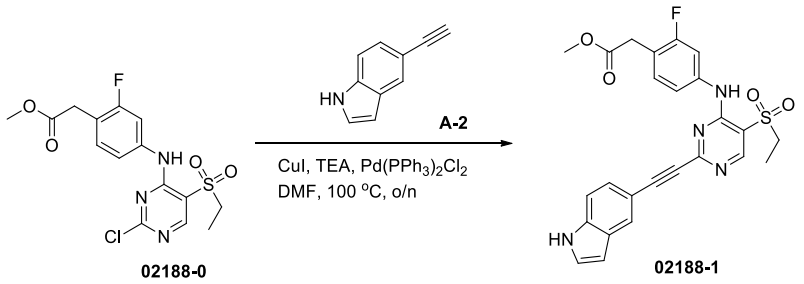
A-1 A-2

To a solution of 5-((trimethylsilyl)ethynyl)-1H-indole (810 mg, 3.80 mmol) in MeOH (10 mL) was added K_2CO_3 (787 mg, 5.70 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred at room temperature under nitrogen atmosphere for 3 hours. After the starting material was consumed, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was obtained as a brown solid (525 mg, 98% yield) and used directly for the next step.

ESI-MS *m/z* calcd for $[C_{10}H_7N]$ $[M+H]^+$: 142.1; found: 142.0

2.3

Methyl-2-(4-((2-((1H-indol-5-yl)ethynyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02188-1)



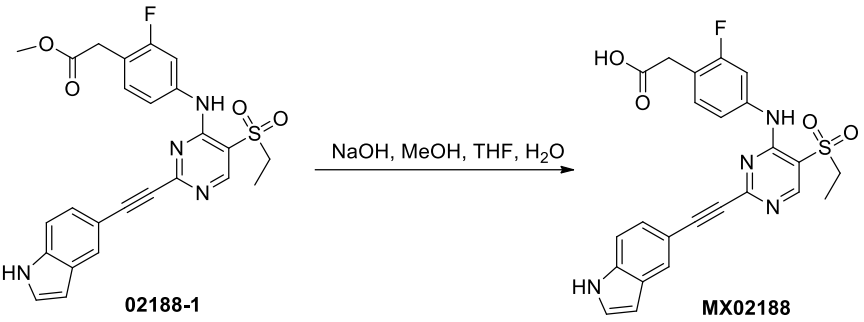
02188-0 02188-1

To a solution of 5-ethynyl-1H-indole (37 mg, 0.26 mmol) in DMF (5 mL) were added 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (100 mg, 0.26 mmol), CuI (5 mg, 0.026 mmol), TEA (53 mg, 0.52 mmol) and $Pd(PPh_3)_2Cl_2$ (6 mg, 0.008 mmol) at 100°C under nitrogen atmosphere. The mixture was stirred at 100°C under nitrogen atmosphere overnight. After the starting material was consumed, the reaction was quenched with water (20 mL) and extracted with EA (30 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/hexane = 0:1 to 1:10, silica gel CS 20 g, 20 mL/min, silica gel, UV 254) to afford a yellow solid product (31 mg, 24% yield).

ESI-MS *m/z* calcd for $[C_{25}H_{21}FN_4O_4S]$ $[M+H]^+$: 493.1; found: 492.7

2.4

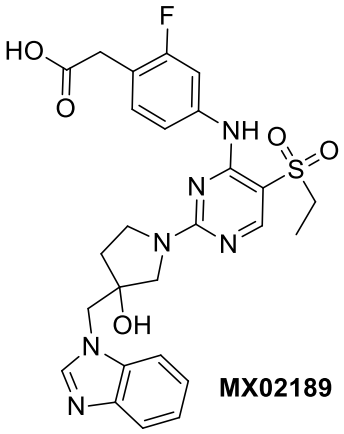
2-(4-((2-((1H-indol-5-yl)ethynyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02188)



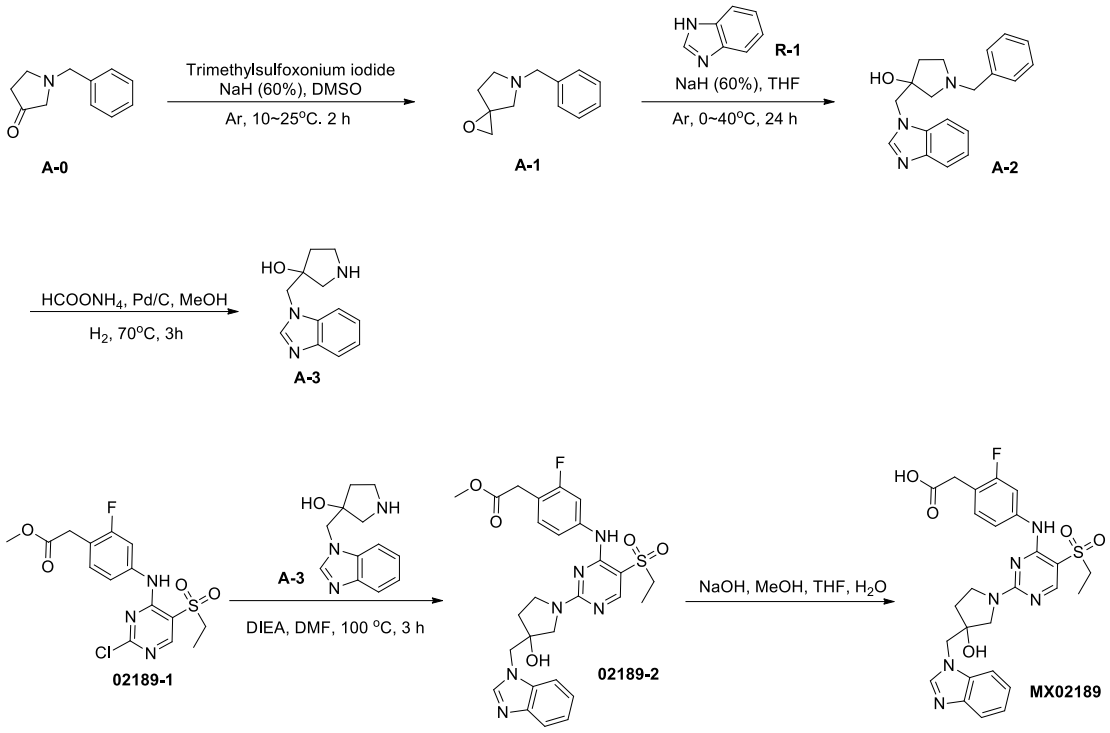
To a solution of 2-(4-((2-((1H-indol-5-yl)ethynyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (31 mg, 0.06 mmol) in MeOH/THF (2 mL, v/v 1:1) was added 2N NaOH aqueous solution at room temperature to adjust the pH to 12. The mixture was stirred under nitrogen atmosphere at room temperature for 3 hours. After the starting material was consumed, the pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L HCOOH), X-Select, 10 μm, 19 × 250 mm, 20 mL/min, UV 254) to afford a pale yellow solid product (2.18 mg, 7% yield).

ESI-MS *m/z* calcd for $[C_{24}H_{19}FN_4O_4S]$ $[M+H]^+$: 479.1; found: 479.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (brs, 1H), 11.50 (s, 1H), 9.15 – 9.11 (m, 1H), 8.68 (s, 1H), 7.92 (s, 1H), 7.62 (d, J = 11.2 Hz, 1H), 7.50 – 7.48 (m, 2H), 7.39 – 7.32 (m, 3H), 6.53 (s, 1H), 3.62 (s, 2H), 3.54 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H).



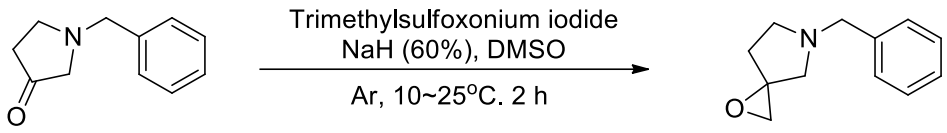
1. Synthetic scheme:



2. Experimental section:

2.1

5-Benzyl-1-oxa-5-azaspiro[2.4]heptane(A-0)



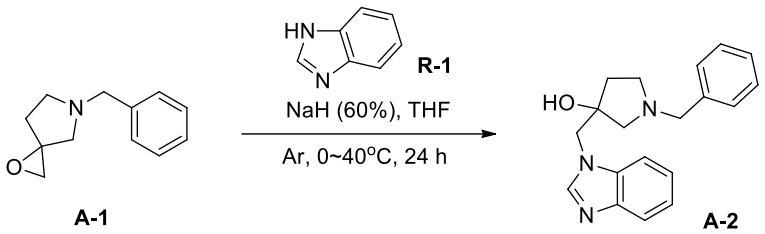
A-0 **A-1**

To a solution of NaH (60%, 300 mg, 7.41 mmol) in DMSO (10 mL), trimethylsulfonium iodide (1.38 g, 6.27 mmol) was added portionwise at 0 °C. The resulting mixture was stirred at 25 °C under an argon atmosphere for 1 h, followed by the addition of 1-benzylpyrrolidin-3-one (1.0 g, 5.7 mmol) in DMSO (11 mL). The reaction mixture was then stirred at 25 °C for an additional 2 hours. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted four times with EA (50 mL). The combined organic layers were washed with saturated saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0–1/1, silica gel-CS 40 g, flow rate 40 mL/min, silica gel, UV 254 detection) to afford a yellow oil (326 mg, 30.2% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{15}NO]$ $[M+H]^+$: 190.1; found: 190.1

2.2

3-((1H-benzo[d]imidazol-1-yl)methyl)-1-benzyl-3-pyrolidinol(A-2)

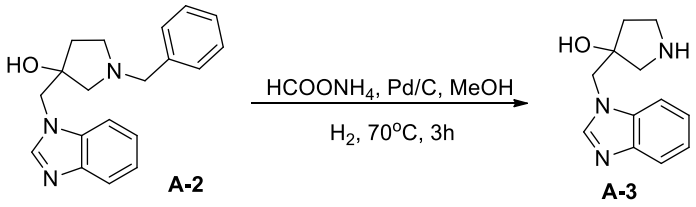


To a solution of NaH (60%, 96 mg, 2.4 mmol) in THF (6 mL) was added portionwise 1H-benzo[d]imidazole (142 mg, 1.2 mmol) at 0 °C. The mixture was stirred at 0 °C under an argon atmosphere for 1 h. Subsequently, a solution of 5-benzyl-1-oxa-5-azaspiro[2.4]heptane (226 mg, 1.2 mmol) in THF (4 mL) was added and the reaction mixture was stirred at 40 °C for 24 h. The reaction was quenched with water (20 mL) and extracted three times with EA (50 mL). The combined organic layers were washed with saturated saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH/DCM = 0–1/9, silica gel-CS 40 g, flow rate 40 mL/min, silica gel, UV 254 detection) to afford colorless oil (245 mg, 66.7% yield)

ESI-MS *m/z* calcd for $[C_{19}H_{21}N_3O]$ $[M+H]^+$: 308.2; found: 308.2

2.3

3-((1H-benzo[d]imidazol-1-yl)methyl)pyrrolidin-3-ol(A-3)

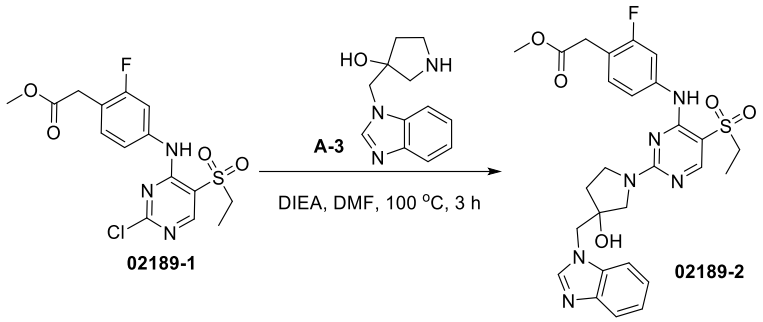


To a solution of 3-((1H-benzo[d]imidazol-1-yl)methyl)-1-benzylpyrrolidin-3-ol (100 mg, 0.33 mmol) and $HCOONH_4$ (250 mg, 3.96 mmol) in MeOH (20 mL) was added Pd/C (30 mg). The mixture was stirred under a hydrogen atmosphere at 70 °C for 3 hours. After cooling, the reaction mixture was filtered under reduced pressure and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse-phase column chromatography ($MeCN/H_2O$ = 0–3/17, C18 column, flow rate 50 mL/min, UV 214 detection) to afford a pale yellow solid (40 mg, 56.6% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{15}N_3O]$ $[M+H]^+$: 218.1; found: 218.1

2.4

Methyl-2-(4-((2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (02189-2)

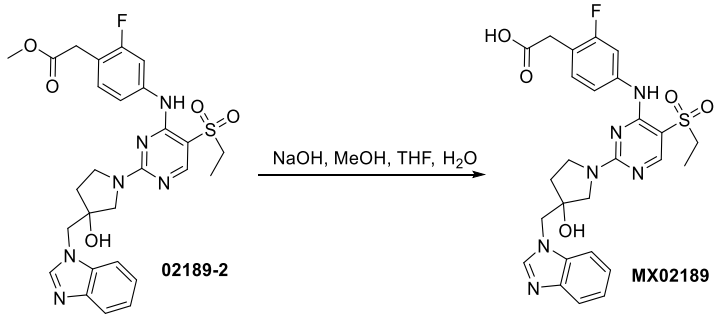


To a solution of 3-((1H-benzo[d]imidazol-1-yl)methyl)pyrrolidin-3-ol (22 mg, 0.10 mmol) and methyl 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (40 mg, 0.10 mmol) in DMF (2 mL) was added DIEA (40 mg, 0.31 mmol). The mixture was stirred at 100 °C under an argon atmosphere for 3 hours. After cooling, the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0–1/1, silica gel-CS 20 g, flow rate 20 mL/min, silica gel, UV 254 detection) to afford a white solid (55 mg, 94% yield).

ESI-MS *m/z* calcd for $[C_{27}H_{29}FN_6O_5S]$ $[M+H]^+$: 569.2; found: 568.8

2.5

2-(4-((2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (MX02189)

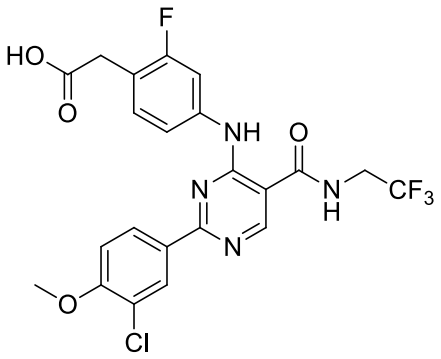


To a solution of methyl 2-(4-((2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (55 mg, 0.10 mmol) in MeOH/THF (2 mL, v/v = 1/1) was added 2N NaOH aqueous solution to adjust the pH to 12. The mixture was stirred under a nitrogen atmosphere at room temperature for 3 hours until the starting material was consumed. The pH was then adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated and the crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L HCOOH), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (42.2 mg, 79% yield).

ESI-MS *m/z* calcd for $[C_{26}H_{27}FN_6O_5S]$ $[M+H]^+$: 555.2; found: 555.2

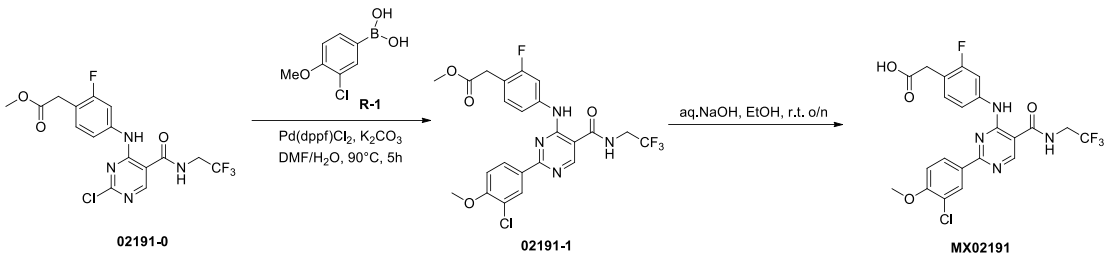
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (brs, 1H), 8.97 – 8.93 (m, 1H), 8.56 – 8.50 (m,

1H), 8.36 – 8.31 (m, 1H), 7.83 – 7.56 (m, 3H), 7.37 – 7.06 (m, 4H), 5.51 (d, *J* = 4.4 Hz, 1H), 4.61 – 4.51 (m, 2H), 3.84 – 3.75 (m, 1H), 3.71 – 3.59 (m, 4H), 3.57 (d, *J* = 11.2 Hz, 1H), 3.51 – 3.45 (m, 2H), 2.22 – 2.10 (m, 1H), 1.93 – 1.82 (m, 1H), 1.91 – 1.15 (m, 3H).



MX02191

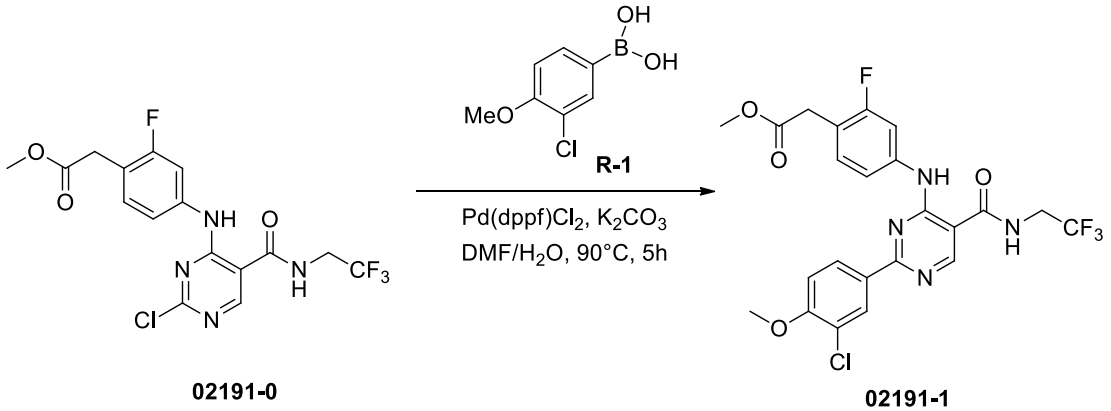
1. Synthetic scheme:



2. Experimental section:

2.1

Methyl-2-(4-((2-(3-chloro-4-methoxyphenyl)-5-((2,2,2-trifluoroethyl)aminocarbonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02191-1)



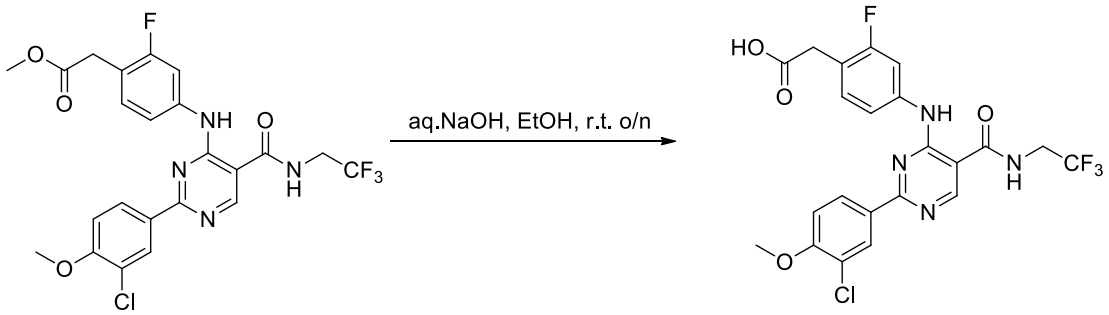
To a solution of methyl 2-(4-((2-chloro-5-((2,2,2-trifluoroethyl)carbamoyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (80 mg, 0.19 mmol) in DMF/water (4 mL, v/v = 3/1) was added (3-chloro-4-methoxyphenyl)boronic acid (35.4 mg, 0.19 mmol), K_2CO_3 (78.8 mg, 0.57 mmol), and $Pd(dppf)Cl_2$ (15.3 mg, 0.021 mmol). The mixture was stirred under a nitrogen

atmosphere at 90 °C for 5 hours until the starting material was consumed. Water (20 mL) was then added, and the mixture was extracted three times with (EA (20 mL). The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (46 mg, 45.9% yield).

ESI-MS *m/z* calcd for $[C_{23}H_{19}ClF_4N_4O_4]$ $[M+H]^+$: 527.1; found: 527.0

2.2

2-(4-((2-(4,5-Dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5-((2,2,2-trifluoroethyl)aminocarbonyl)pyrimidin-4-yl)amino)-2-fluorophenyl) Acetic acid (MX02191)

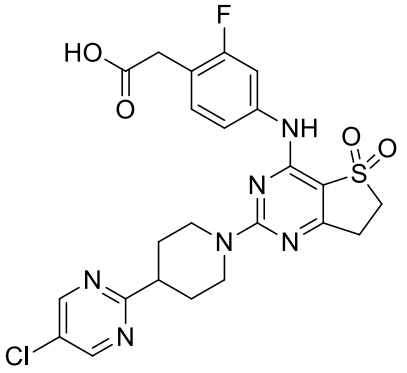


02191-1 MX02191

To a solution of methyl 2-(4-((2-(3-chloro-4-methoxyphenyl)-5-((2,2,2-trifluoroethyl)carbamoyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (46 mg, 0.087 mmol) in EtOH (2 mL) was added 1N NaOH (0.6 mL, 0.6 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature overnight until the starting material was consumed. The pH was then adjusted to pH = 6 with 1N HCl aqueous solution. The mixture was concentrated under reduced pressure, and the crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (7.17 mg, 16% yield).

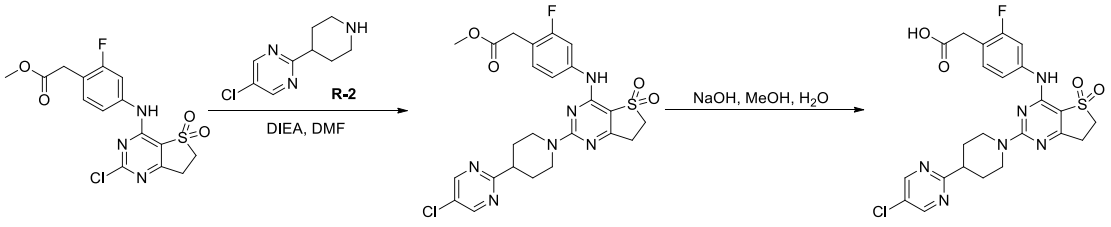
ESI-MS *m/z* calcd for $[C_{22}H_{17}ClF_4N_4O_4]$ $[M+H]^+$:513.1; found: 512.5

^1H NMR (400 MHz, DMSO-d_6) δ 11.10 (br, 1H), 9.59 (br, 1H), 9.00 (s, 1H), 8.33 (d, J = 2.0 Hz, 1H), 8.29 (dd, J = 8.4, 1.6 Hz, 1H), 7.83 (d, J = 12.8 Hz, 1H), 7.36 – 7.32 (m, 3H), 4.17 (q, J = 9.6 Hz, 2H), 3.95 (s, 3H), 3.53 (s, 2H).



MX02206

1. Synthetic scheme:

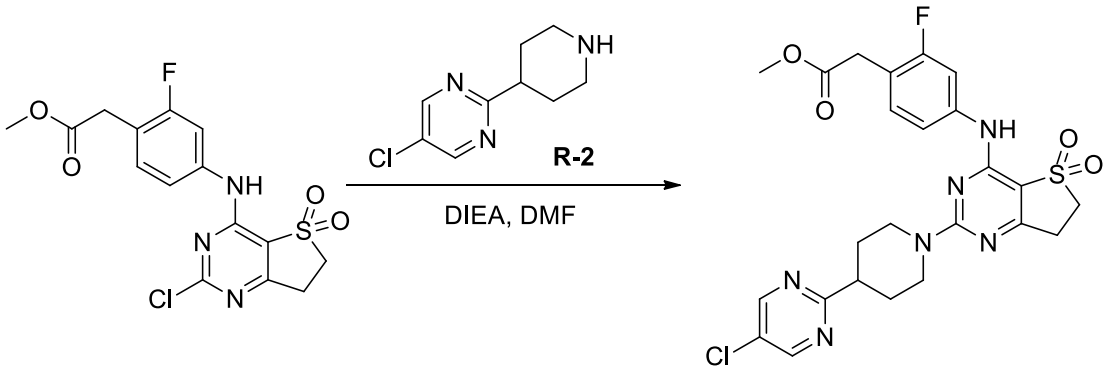


02206-0 **02206-1** **MX02206**

2. Experimental section:

2.1

Methyl-2-(4-((2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02206-1)



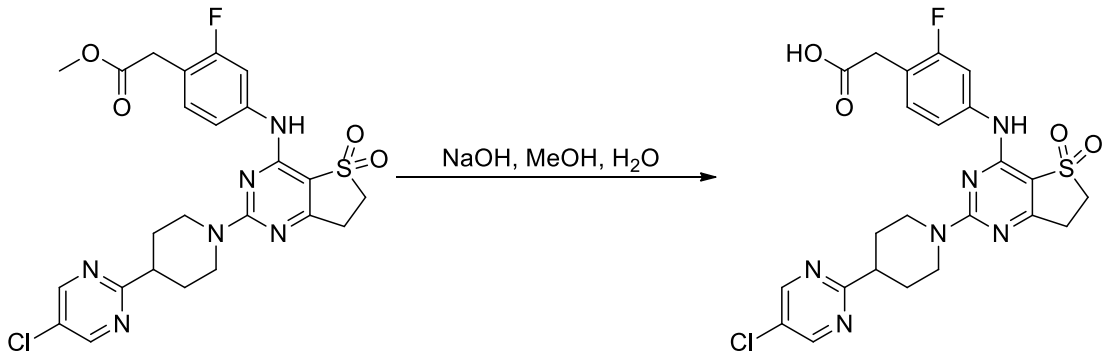
02206-0 **02206-1**

To a solution of methyl 2-(4-((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (50 mg, 0.13 mmol) in DMF (3 mL) was added DIEA (67 mg, 0.52 mmol), followed by 5-chloro-2-(piperidin-4-yl)pyrimidine (51 mg, 0.26 mmol). The mixture was stirred at 90 °C for 1 hour. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a yellow solid (30 mg, 42.32% yield).

ESI-MS *m/z* calcd for $[C_{24}H_{24}ClFN_6O_4S]$ $[M+H]^+$:547.1; found: 547.8

2.2

2-(4-((2-(4-(5-chloro-2-pyrimidinyl)piperidin-1-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02206)

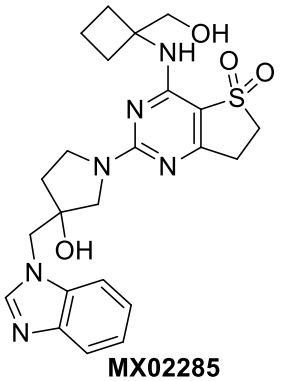


02206-1 MX02206

To a solution of methyl 2-(4-((2-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (30 mg, 0.055 mmol) in MeOH (3 mL) was added a solution of NaOH (11 mg, 0.27 mmol) in water (1 mL). The mixture was stirred at room temperature for 2 hours. The pH was adjusted to 6 with AcOH. The mixture was filtered, and the filtrate was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (15.11 mg, 51.69% yield).

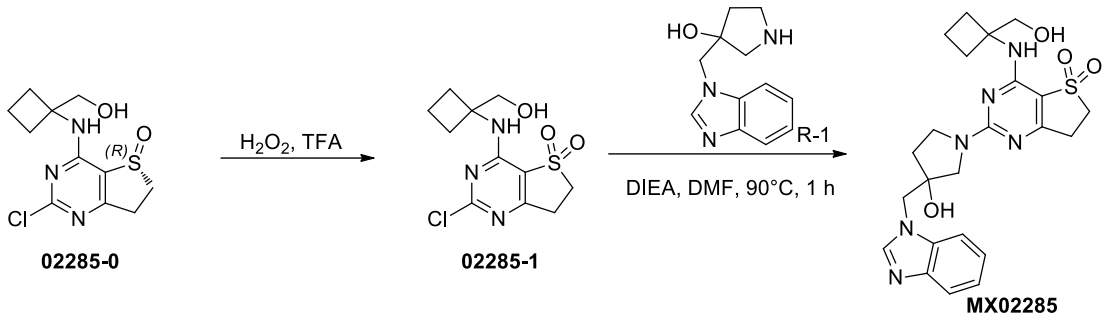
ESI-MS *m/z* calcd for $[C_{23}H_{22}ClFN_6O_4S]$ $[M+H]^+$:533.1; found: 532.8

^1H NMR (400 MHz, DMSO-d_6) δ8.87 (s, 2H), 7.50 (dd, *J* = 12.0, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.22 (t, *J* = 8.8 Hz, 1H), 4.74 – 4.54 (m, 2H), 3.55 (t, *J* = 7.2 Hz, 2H), 3.42 (s, 2H), 3.25 – 3.13 (m, 5H), 2.03 – 2.00 (m, 2H), 1.74 – 1.68 (m, 2H).



MX02285

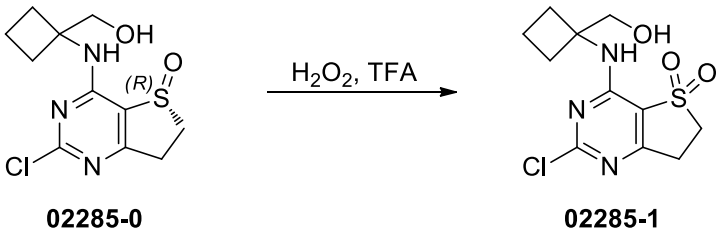
1. Synthetic scheme:



2. Experimental section:

2.1

2-Chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5,5-dioxide(02285-1)

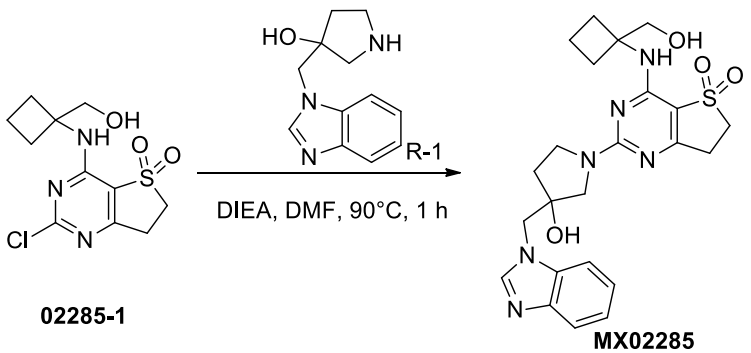


To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (100 mg, 0.35 mmol) in TFA (1.5 mL) was added hydrogen peroxide (30%, 0.1 mL). The mixture was stirred at room temperature for 16 hours. The mixture was poured into a mixture of ice and aqueous ammonia. The mixture was extracted twice with DCM (30 mL). The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. A white solid was obtained (92 mg, 87.15% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{14}ClN_3O_3S]$ $[M+H]^+$:304.0; found: 304.0

2.2

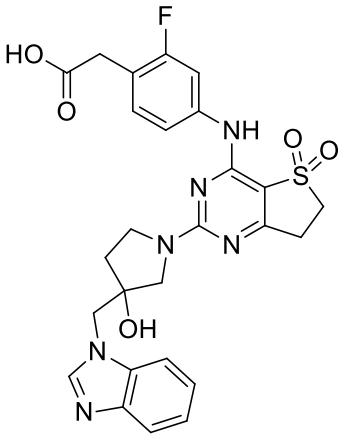
2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6, 7-dihydrothieno[3,2-d]pyrimidine 5,5-dioxide(MX02285)



To a solution of 2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5,5-dioxide (40 mg, 0.13 mmol) in DMF (3 mL) was added 3-((1H-benzo[d]imidazol-1-yl)methyl)pyrrolidin-3-ol (40 mg, 0.18 mmol) and DIEA (68 mg, 0.53 mmol). The mixture was stirred at 90 °C for 2 hours. The mixture was concentrated under reduced pressure, and the crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (19.35 mg, 30.33% yield).

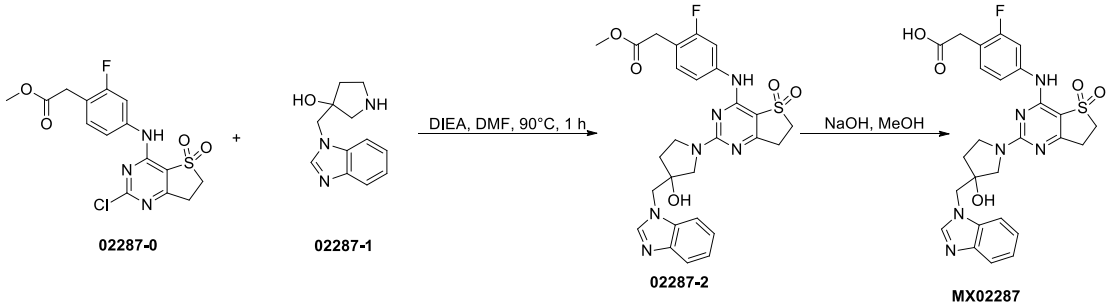
ESI-MS *m/z* calcd for $[C_{23}H_{28}N_6O_4S]$ $[M+H]^+$:485.2; found: 485.0

^{1}H NMR (400 MHz, Methanol-d_4) δ8.21 – 8.20 (m, 1H), 7.68 – 7.64 (m, 2H), 7.34 – 7.26 (m, 2H), 4.59 – 4.46 (m, 2H), 3.90 – 3.65 (m, 5H), 3.55 – 3.35 (m, 3H), 3.13 – 3.05 (m, 2H), 2.43 – 2.41 (m, 1H), 2.29 – 2.19 (m,3H), 2.03 – 1.93 (m, 3H), 1.73 – 1.68 (m, 1H).



MX02287

1. Synthetic scheme:

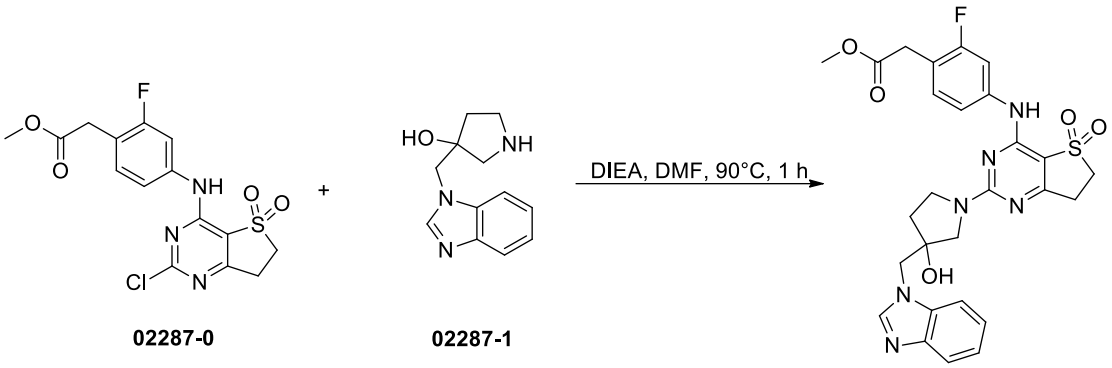


02287-0 02287-1 02287-2 MX02287

2. Experimental section:

2.1

Methyl-2-(4-((2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester(02287-2)



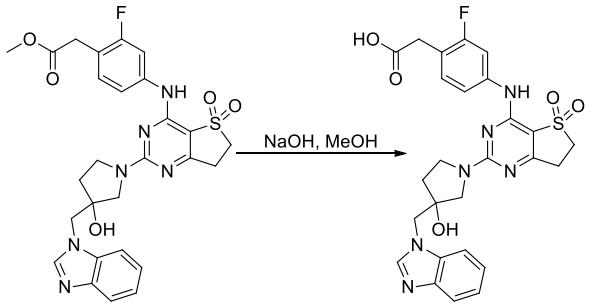
02287-0 02287-1 02287-2

To a solution of 3-((1H-benzo[d]imidazol-1-yl)methyl)pyrrolidin-3-ol (40.5 mg, 0.19 mmol) and methyl 2-(4-((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (60 mg, 0.16 mmol) in DMF (3 mL) was added DIEA (40 mg, 0.31 mmol). The mixture was stirred at 90 °C under an argon atmosphere for 1 hour. After cooling, the mixture was concentrated under reduced pressure. The crude product was purified by reversed-phase column chromatography (MeCN/H_2O = 0–40%, C18 column, 40 g, flow rate 50 mL/min, UV 254 detection) to afford a white solid (31 mg, 35.18% yield).

ESI-MS *m/z* calcd for $[C_{27}H_{27}FN_6O_5S]$ $[M+H]^+$: 567.2; found: 567.9

2.2

2-(4-((2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-5, 5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(MX02287)



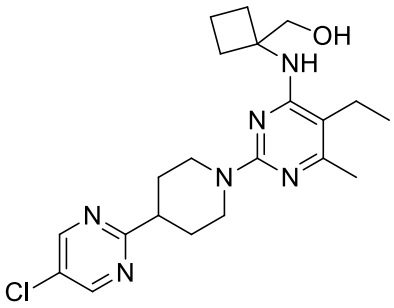
022287-2 MX02287

Methyl 2-(4-((2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-5,5-dioxo-6, 7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid methyl ester (31 mg, 0.055 mmol) was added to a solution of NaOH (10.9 mg, 0.27 mmol) in water (1 mL) in a solution of the compound in MeOH (3 mL). The mixture was then stirred at room temperature for 2 hours. The pH of the solution was adjusted to 6 with AcOH. The mixture was filtered, and the filtrate was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19 × 250 mm, 20 mL/min, UV 254] to obtain a white solid product

(15.03 mg, 49.71% yield).

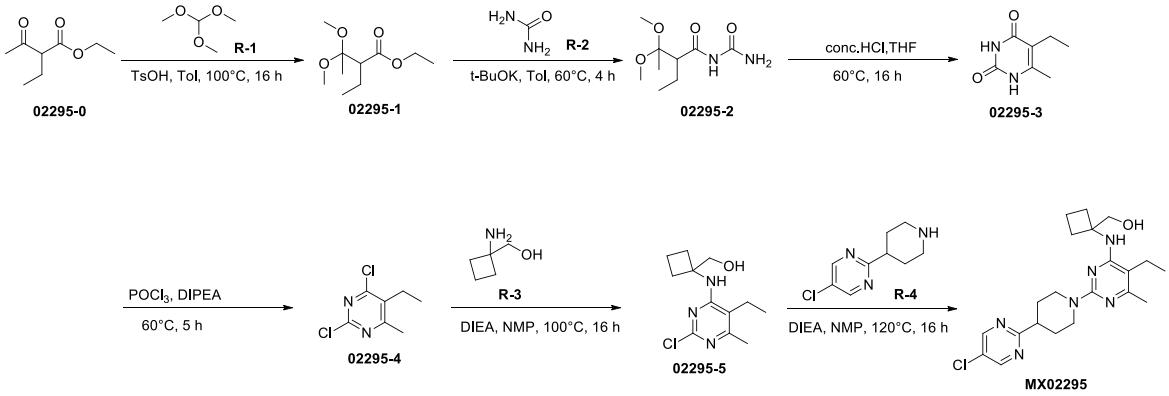
ESI-MS *m/z* calcd for $[C_{26}H_{25}FN_6O_5S]$ $[M+H]^+$:553.2; found: 553.0

^{1}H NMR (400 MHz, Methanol-d_4) δ8.23(s, 1H), 7.78 – 7.62 (m, 2.5H), 7.46 – 7.24 (m, 4H), 7.02 – 6.98 (m, 0.5H), 4.58 – 4.49 (m, 2H), 3.90 – 3.84 (m, 1H), 3.79 – 3.69 (m,2H), 3.61 – 3.47 (m, 5H), 3.23 – 3.13 (m, 2H), 2.28 – 2.19 (m, 1H), 2.01 – 1.96 (m, 1H).



MX02295

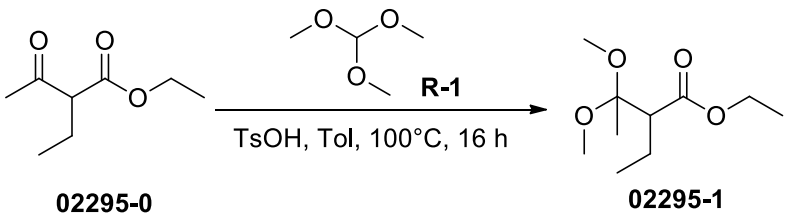
1. Synthetic scheme:



2. Experimental section:

2.1

Ethyl 2-ethyl-3,3-dimethoxybutanoate（02295-1）



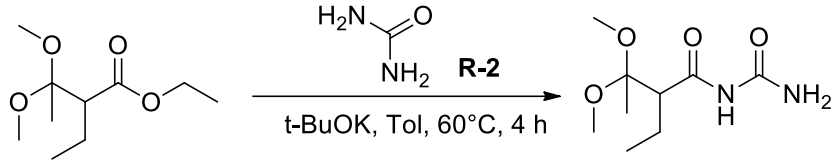
To a solution of ethyl 2-ethyl-3-oxobutanoate (3.2 g, 20.2 mmol) in toluene (40 mL) was added trimethyl orthoformate (2.58 g, 24.2 mmol) and *p*-toluenesulfonic acid (694 mg, 4.04 mmol). The mixture was stirred at 100 °C for 16 hours. After cooling, the solvent was removed under reduced pressure. Water (50 mL) was added, and the mixture was extracted three times with DCM (50 mL). The combined organic layers were dried over anhydrous sodium sulfate,

filtered and concentrated under reduced pressure to afford a yellow liquid crude product (4.2 g, 100% yield).

ESI-MS *m/z* calcd for $[C_{10}H_{20}O_4]$ $[M+H]^+$: 205.1; found: 204.3

2.2

N-Formyl-2-ethyl-3,3-dimethoxybutanamide（02295-2）



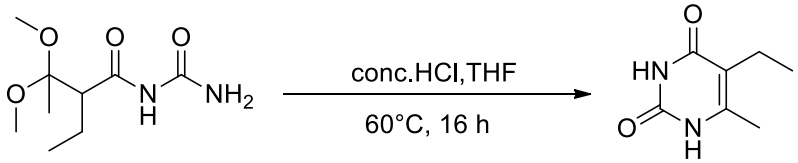
02295-1 02295-2

To a solution of ethyl 2-ethyl-3,3-dimethoxybutanoate (4.2 g, 20.2 mmol) in toluene (40 mL) was added urea (1.21 g, 20.2 mmol) and t-BuOK (2.26 g, 20.2 mmol). The mixture was stirred at 60 °C for 4 hours. After cooling, the solvent was removed under reduced pressure. Water (50 mL) was added, and the mixture was extracted three times with DCM (50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford a yellow liquid crude product (3.6 g, 81.8% yield).

ESI-MS *m/z* calcd for $[C_9H_{18}N_2O_4]$ $[M+H]^+$: 219.1; found: 219.0

2.3

5-Ethyl-6-methylpyrimidine-2,4(1H,3H)-dione（02295-3）



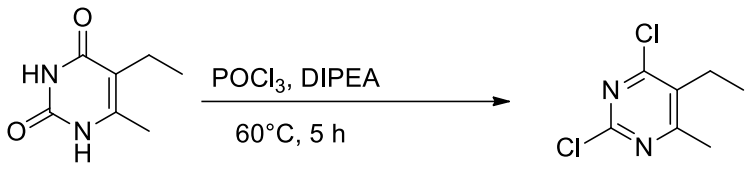
02295-2 02295-3

To a solution of *N*-carbamoyl-2-ethyl-3,3-dimethoxybutanamide (3.6 g, 16.5 mmol) in THF (40 mL) was added concentrated HCl (8.3 mL, 100 mmol). The mixture was stirred at 60 °C for 16 hours. After cooling, the solvent was removed under reduced pressure. Water (50 mL) was added, and the mixture was extracted three times with DCM (50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH = 1/0–5/1, silica gel-CS 20 g, flow rate 30 mL/min, silica gel, UV 254 detection) to afford a yellow solid (550 mg, 21.6% yield).

ESI-MS *m/z* calcd for $[C_7H_{10}N_2O_2]$ $[M+H]^+$: 155.1; found: 155.4

2.4

2,4-Dichloro-5-ethyl-6-methylpyrimidine（02295-4）



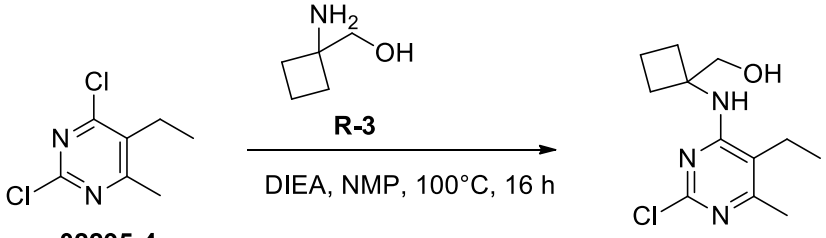
02295-3 **02295-4**

To a solution of 5-ethyl-6-methylpyrimidine-2,4(1H,3H)-dione (400 mg, 2.6 mmol) in $POCl_3$ (4 mL) was added DIPEA (33.6 mg, 0.26 mmol). The mixture was stirred at 60 °C for 5 hours. After cooling, the solvent was removed under reduced pressure. Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the mixture was extracted three times with DCM (20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0–30%, silica gel-CS 12 g, flow rate 30 mL/min, silica gel, UV 254 detection) to afford a yellow solid (375 mg, 76.0% yield).

ESI-MS *m/z* calcd for $[C_7H_8Cl_2N_2]$ $[M+H]^+$: 191.0; found: 191.2

2.5

(1-((2-Chloro-5-ethyl-6-methylpyrimidin-4-yl)amino)cyclobutyl)methanol(02295-5)



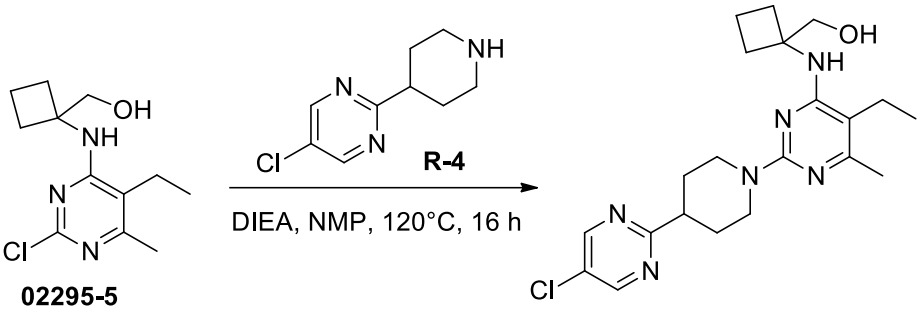
02295-4 **02295-5**

To a solution of 2,4-dichloro-5-ethyl-6-methylpyrimidine (191 mg, 1 mmol) in NMP (3 mL) and DIEA (0.5 mL) was added (1-aminocyclobutyl)methanol (101 mg, 1 mmol). The mixture was stirred at 100 °C for 16 hours. After cooling, the solvent was removed under reduced pressure. Water (10 mL) was added, and the mixture was extracted three times with DCM (10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0–100%, silica gel-CS 12 g, flow rate 30 mL/min, silica gel, UV 254 detection) to afford a yellow solid (85 mg, 33.1% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{18}ClN_3O]$ $[M+H]^+$: 256.1; found: 256.1

2.6

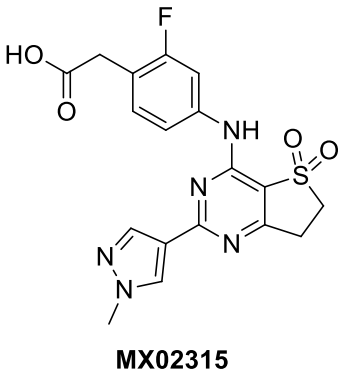
(1-((2-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-5-ethyl-6-methylpyrimidin-4-yl)amino)cyclobutyl)methanol(MX02295)



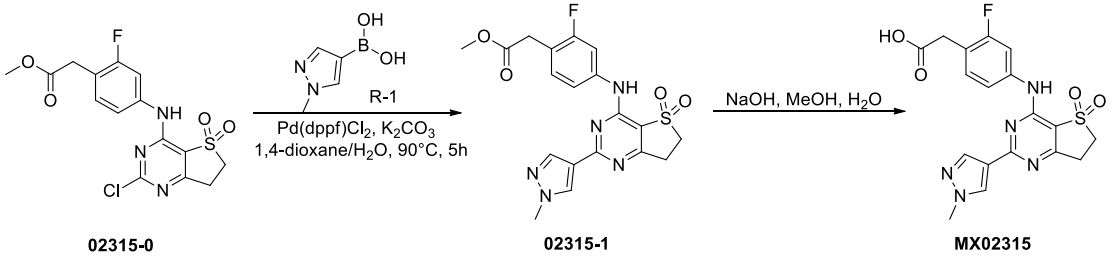
To a solution of (1-((2-chloro-5-ethyl-6-methylpyrimidin-4-yl)amino)cyclobutyl)methanol (85 mg, 0.332 mmol) in NMP (3 mL) was added 5-chloro-2-(piperidin-4-yl)pyrimidine (131.0 mg, 0.664 mmol) and DIEA (1 mL). The reaction mixture was stirred at 100 °C for 16 hours. The solvent was removed under reduced pressure, and the crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (34 mg, 24.5% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{29}ClN_6O]$ $[M+H]^+$: 417.2; found: 417.3

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 2H), 5.93 (s, 1H), 4.80 (t, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 12.8 Hz, 2H), 3.69 (d, *J* = 5.6 Hz, 2H), 3.12 – 3.07 (m, 1H), 2.89 – 2.83 (m, 2H), 2.41 – 2.31 (m, 2H), 2.28 – 2.23 (m, 2H), 2.15 – 2.08 (m, 5H), 1.89 – 1.87 (m, 2H), 1.79 – 1.72 (m, 2H), 1.66 – 1.56 (m, 2H)， 0.97 (t, *J* = 7.2 Hz, 3H).



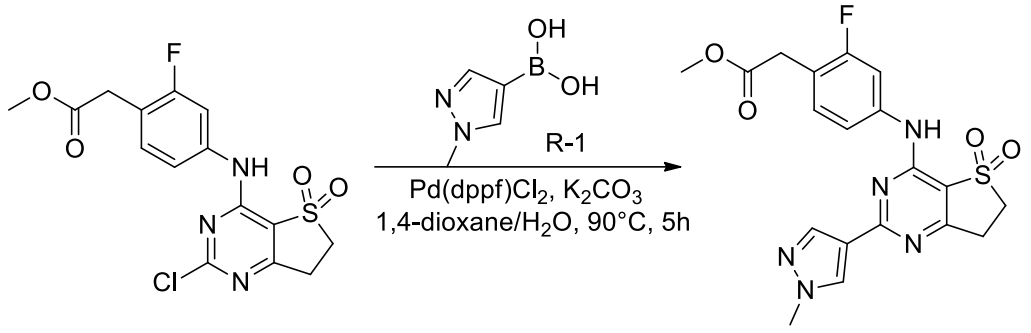
1. Synthetic scheme:



2. Experimental section:

2.1

Methyl-2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetate(02315-1)



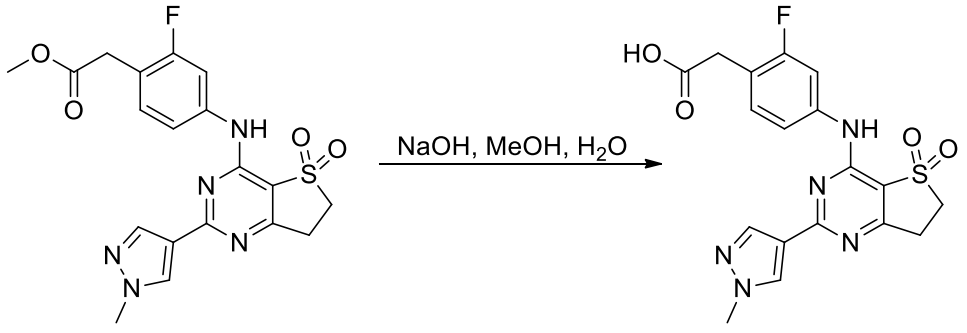
02315-0 02315-1

To a solution of methyl 2-(4-((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (120 mg, 0.31 mmol) in 1,4-dioxane/H_2O (10 mL, v/v = 4/1) was added (1-methyl-1H-pyrazol-4-yl)boronic acid (58.7 mg, 0.47 mmol), K_2CO_3 (172 mg, 1.24 mmol), and $Pd(dppf)Cl_2$ (25.4 mg, 0.031 mmol). The mixture was stirred at 90 °C under a nitrogen atmosphere for 5 hours. After consumption of the starting material, the reaction mixture was quenched with water and extracted three times with EA (20 mL). The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH = 0–10%, silica gel-CS 20 g, flow rate 20 mL/min, silica gel, UV 254 detection) to afford a yellow solid (66 mg, 49.18% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{18}FN_5O_4S]$ $[M+H]^+$:432.1; found: 432.0

2.2

2-(2-Fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid(MX02315)



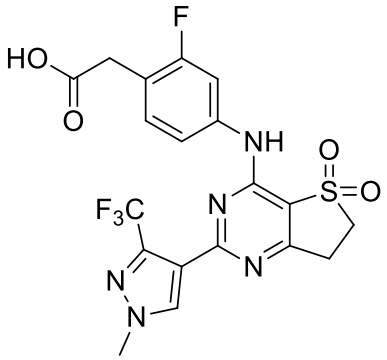
02315-1 MX02315

To a solution of methyl 2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetate (66 mg, 0.15 mmol) in MeOH (3 mL) was added a solution of NaOH (31 mg, 0.77 mmol) in water (1 mL). The mixture was

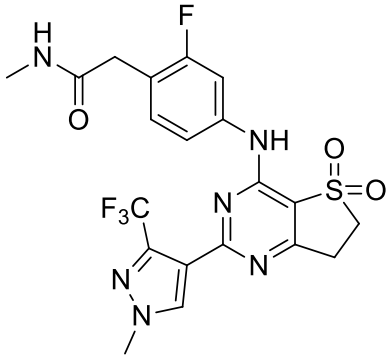
stirred at room temperature for 2 h. The pH was adjusted to 6 with AcOH. The mixture was filtered, and the filtrate was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (40 mg, 62.64% yield).

ESI-MS *m/z* calcd for $[C_{18}H_{16}FN_5O_4S]$ $[M+H]^+$:418.1; found: 418.0

^1H NMR (400 MHz, Methanol-d_4) δ 8.21 (s, 1H), 8.05 (s, 1H), 7.62 (dd, *J* = 11.8, 2.0 Hz, 1H), 7.43 (dd, *J* = 11.8, 2.0 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.65 – 3.61 (m, 4H), 3.39 – 3.36 (m, 2H).

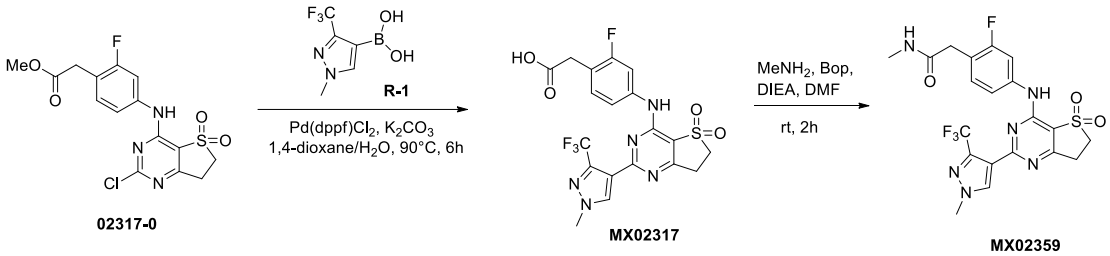


MX02317



MX02359

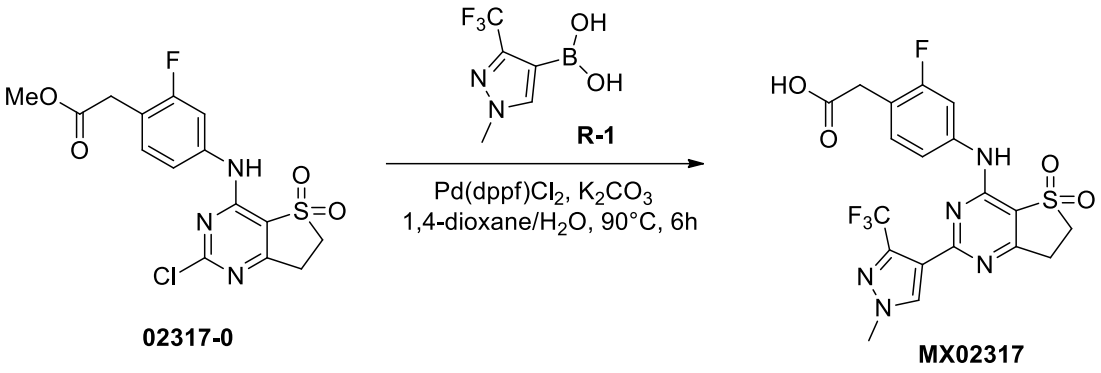
1. Synthetic scheme:



2. Experimental section:

2.1

2-(2-Fluoro-4-((2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid(MX02317)



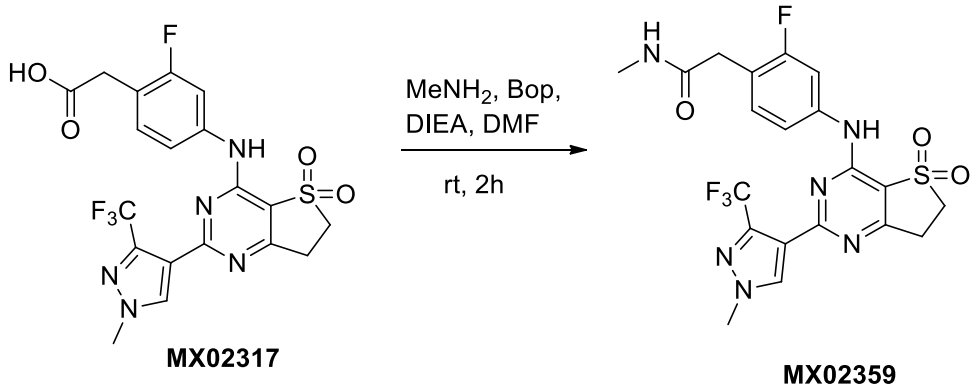
To a solution of methyl 2-(4-((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (100 mg, 0.259 mmol) in 1,4-dioxane/water (12.5 mL, v/v = 4/1) was added (1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)boronic acid (56 mg, 0.285 mmol), K_2CO_3 (108 mg, 0.777 mmol), and $Pd(dppf)Cl_2$ (19 mg, 0.026 mmol). The mixture was heated to 90 °C and stirred under a nitrogen atmosphere for 6 hours. After cooling, water (10 mL) was added, and the mixture was extracted three times with DCM (30 mL). The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L HCOOH), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (30 mg, 24% yield).

ESI-MS m/z calcd for $[C_{19}H_{15}F_4N_5O_4S]$ [M+H]+: 486.1; found: 486.0

1H NMR (400 MHz, Methanol-d_4) δ 8.33 (s, 1H), 7.51 – 7.47 (m, 1H), 7.34 – 7.33 (m, 2H), 3.99 (s, 3H), 3.66 – 3.63 (m, 4H), 3.38 (t, J = 7.0 Hz, 2H)

2.2

2-(2-Fluoro-4-((2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl) -N-methylacetamide(MX02359)

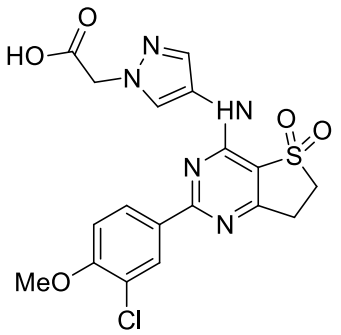


To a solution of 2-(2-fluoro-4-((2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid (21 mg, 0.044 mmol) in DMF (2 mL) was added 2M methylamine solution in THF (0.04 mL, 0.074 mmol), BOP

(16.4 mg, 0.037 mmol), and DIEA (9.6 mg, 0.074 mmol). The mixture was stirred at room temperature for 2 hours, and then the reaction mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford a white solid (6.8 mg, 55.1% yield).

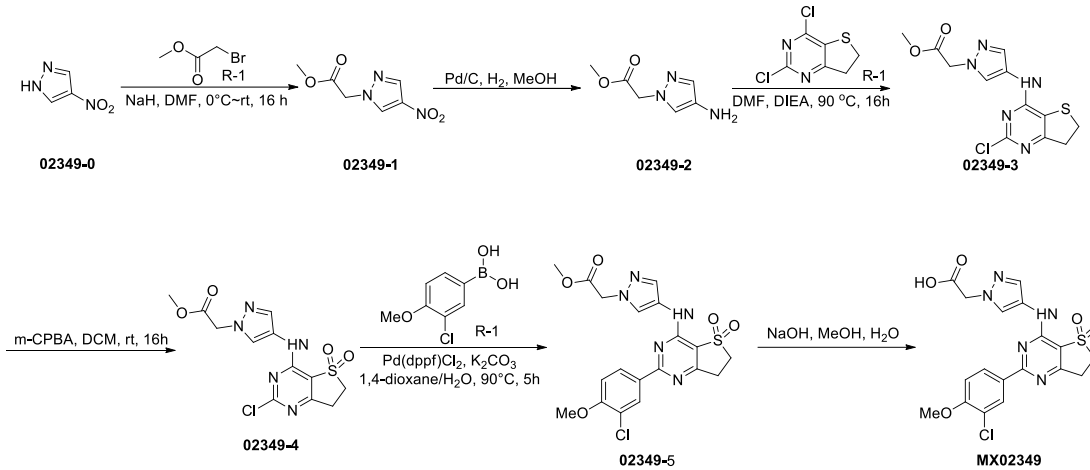
ESI-MS *m/z* calcd for $[C_{20}H_{18}F_4N_6O_3S]$ $[M+H]^+$: 499.1; found: 498.9

^1H NMR (400 MHz, Methanol-d_4) δ 8.34 (s, 1H), 7.52 – 7.49 (m, 1H), 7.34 – 7.32 (m, 2H), 3.98 (s, 3H), 3.65 (t, J = 7.2 Hz, 2H), 3.57 (s, 2H), 3.38 (t, J = 7.2 Hz, 2H), 2.75 (s, 3H)



MX02349

1. Synthetic scheme:

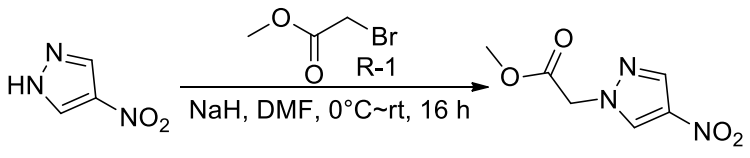


02349-0 02349-1 02349-2 02349-3 02349-4 02349-5 MX02349

2. Experimental section:

2.1

Methyl 2-(4-nitro-1H-pyrazol-1-yl)acetate(02349-1)



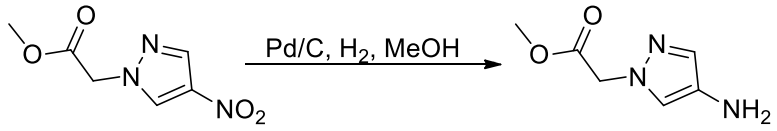
02349-0 **02349-1**

To a solution of 4-nitro-1H-pyrazole (6.0 g, 53.06 mmol) in DMF (50 mL) was added NaH (60%, 2.55 g, 63.68 mmol) at 0 °C. The mixture was stirred at room temperature for 0.5 hours. Methyl 2-bromoacetate (9.74 g, 63.68 mmol) was then added at 0 °C, and the mixture was stirred at room temperature for 16 hours. The mixture was poured into ice water and extracted twice with ethyl acetate (EA, 100 mL). The organic phase was washed with saturated saturated brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0–100%, silica gel-CS 80 g, flow rate 50 mL/min, silica gel, UV 254 detection) to afford a yellow solid (5 g, 50.89% yield).

ESI-MS *m/z* calcd for $[C_6H_7N_3O_4]$ $[M+H]^+$:186.0; found:186.2

2.2

Methyl 2-(4-amino-1H-pyrazol-1-yl)acetate (02349-2)



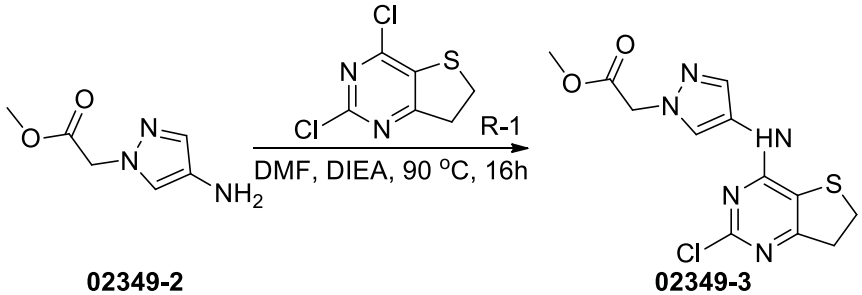
02349-1 **02349-2**

To a solution of methyl 2-(4-nitro-1H-pyrazol-1-yl)acetate (5.0 g, 27.0 mmol) in MeOH (50 mL) was added Pd/C (500 mg, 30% H_2O). The mixture was stirred under a hydrogen atmosphere at room temperature for 16 hours. The reaction mixture was filtered through Celite and washed with MeOH. The filtrate was concentrated to afford a yellow solid (4.1 g, 97.85% yield).

ESI-MS *m/z* calcd for $[C_6H_9N_3O_2]$ $[M+H]^+$:156.1; found:156.2

2.3

Methyl-2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate(02349-3)



02349-2 **02349-3**

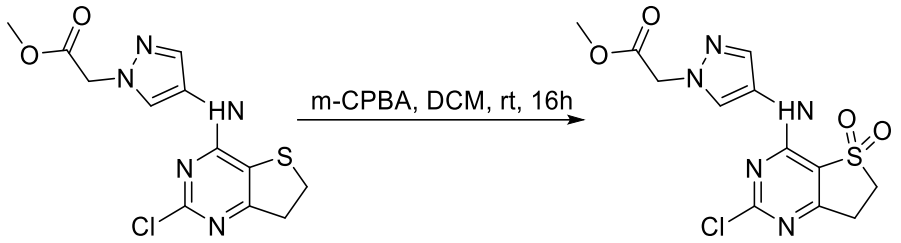
To a solution of methyl 2-(4-amino-1H-pyrazol-1-yl)acetate (450 mg, 2.90 mmol) and 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidine (901 mg, 4.35 mmol) in DMF (10 mL) was

added DIEA (1.5 g, 11.6 mmol). The mixture was stirred at 90 °C for 16 hours, cooled to room temperature, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0–50%, silica gel-CS 20 g, flow rate 25 mL/min, silica gel, UV 254 detection) to afford a yellow solid (220 mg, 23.28% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{12}ClN_5O_2S]$ $[M+H]^+$:326.0; found:326.0

2. 4

Methyl-2-(4-(((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate(02349-4)



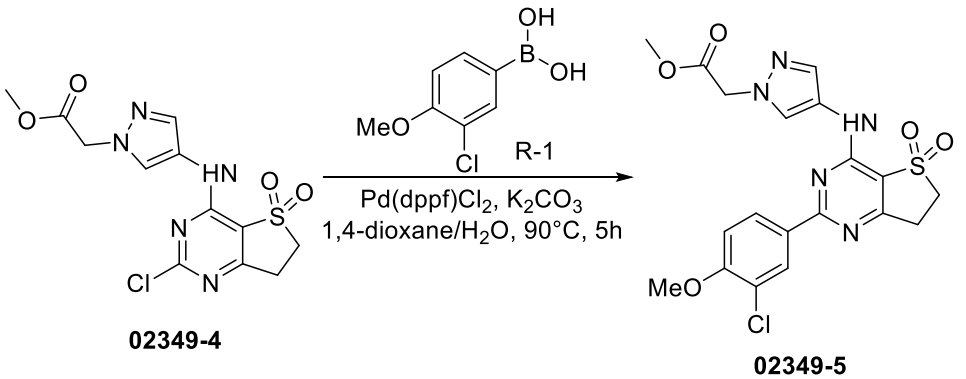
02349-3 **02349-4**

To a solution of methyl 2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate (100 mg, 0.31 mmol) in DCM (10 mL) was added m-CPBA (85%, 249.3 mg, 1.23 mmol). The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL) and extracted twice with DCM (20 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EA/DCM = 0–30%, silica gel-CS 20 g, flow rate 20 mL/min, silica gel, UV 254 detection) to afford the yellow solid (55 mg, 50.08% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{12}ClN_5O_4S]$ $[M+H]^+$:358.0; found:358.0

2.5

Methyl2-(4-((2-(3-chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate(02349-5)



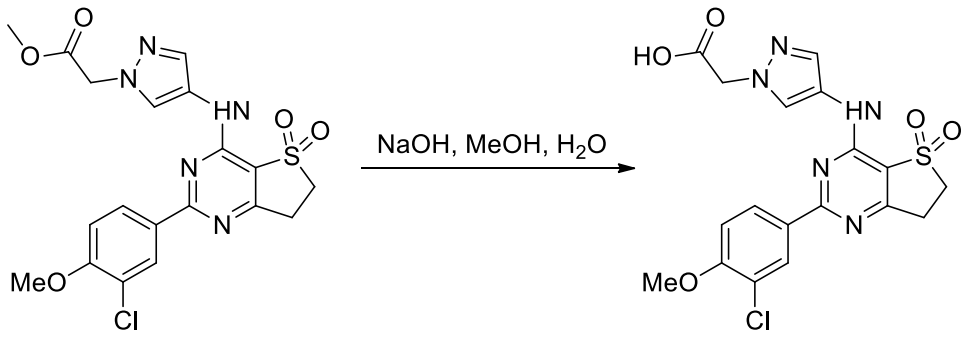
02349-4 **02349-5**

To a solution of methyl 2-(4-((2-chloro-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate (55 mg, 0.15 mmol) in 1,4-dioxane/H_2O (5 mL, v/v = 4/1) was added (3-chloro-4-methoxyphenyl)boronic acid (43.0 mg, 0.23 mmol), K_2CO_3 (85 mg, 0.62 mmol), and Pd(dppf)Cl_2 (12.6 mg, 0.015 mmol). The mixture was stirred at 90 °C under a nitrogen atmosphere for 5 hours. After cooling, the reaction mixture was quenched with water and extracted twice with EA (20 mL). The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (DCM/MeOH = 0–10%, silica gel-CS 20 g, flow rate 20 mL/min, silica gel, UV 254 detection) to afford the yellow solid (33 mg, 46.27% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{18}ClN_5O_5S]$ $[M+H]^+$:464.1; found: 464.0

2.6

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetic acid(MX02349)

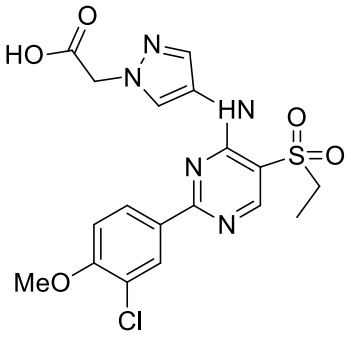


02349-5 **MX02349**

To a solution of methyl 2-(4-((2-(3-chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate (33 mg, 0.071 mmol) in MeOH (3 mL) was added a solution of NaOH (14.2 mg, 0.36 mmol) in water (1 mL). The mixture was stirred at room temperature for 2 hours. The pH was adjusted to 6 with AcOH. The mixture was filtered, and the filtrate was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm column, 19 × 250 mm, flow rate 20 mL/min, UV 254 detection) to afford the white solid (21 mg, 65.62% yield).

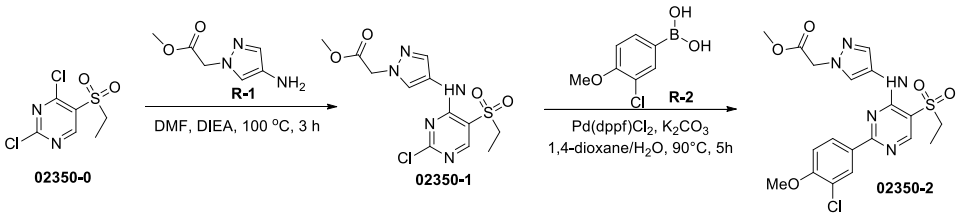
ESI-MS *m/z* calcd for $[C_{18}H_{16}ClN_5O_5S]$ $[M+H]^+$:450.1; found:450.0

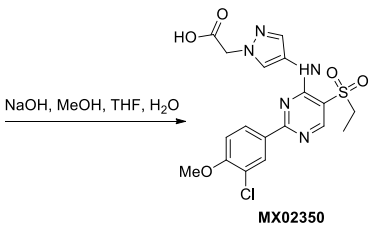
^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ8.39 (d, *J* = 2.0 Hz, 1H), 8.34 (dd, *J* = 8.8， 2.0 Hz, 1H), 8.16 (s, 1H), 7.82 (s, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 4.93 (s, 2H), 3.97 (s, 3H), 3.60 (t, *J* = 6.8Hz, 2H), 3.34 （t, *J* = 7.2 Hz, 2H）.



MX02350

1. Synthetic scheme:

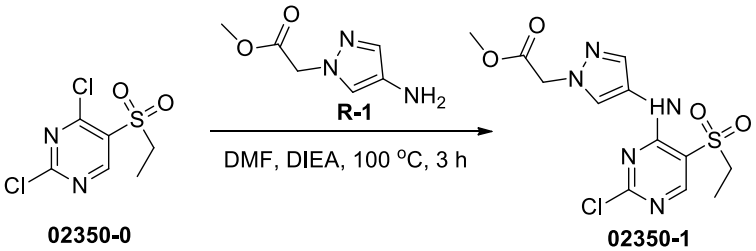




2. Experimental section:

2.1

Methyl2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate(02350-1)



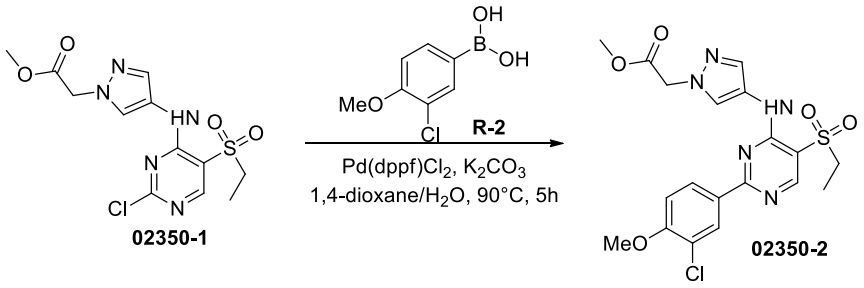
To a solution of 2,4-dichloro-5-(ethylsulfonyl)pyrimidine (80 mg, 0.33 mmol) in DMF (3 mL) was added 2-(4-amino-1H-pyrazol-1-yl)acetic acid methyl ester (51 mg, 0.33 mmol) and DIEA (173 mg, 1.34 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 3 h until the starting material was consumed. Water (20 mL) was added, and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with

saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE= 0/1 to 1/1, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (71 mg, 60% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{14}ClN_5O_4S]$ $[M+H]^+$: 360.1; found: 360.0

2.2

Methyl2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate (02350-2)

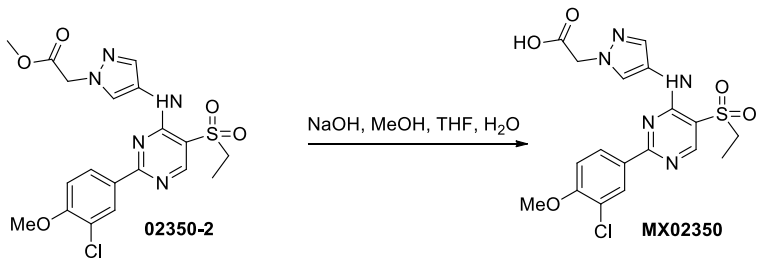


To a solution of methyl 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate (71 mg, 0.20 mmol) in 1,4-dioxane/water (2.5 mL, v/v = 4/1) was added 3-chloro-4-methoxyphenylboronic acid (43 mg, 0.23 mmol), K_2CO_3 (55 mg, 0.40 mmol), and $Pd(dppf)Cl_2$ (14 mg, 0.02 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C for 5 hours until the starting material was consumed. Water (20 mL) was added, and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0/1 to 1/1, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (34 mg, 37% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{20}ClN_5O_5S]$ $[M+H]^+$: 466.1; found: 466.2

2.3

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetic acid(MX02350)

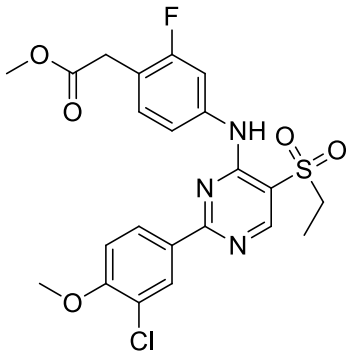


To a solution of methyl 2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetate (34 mg, 0.07 mmol) in

MeOH/THF (2 mL, v/v = 1/1) was added 2N NaOH aqueous solution to adjust the pH to 12. The mixture was stirred under nitrogen at room temperature for 3 hours until the starting material was consumed. The pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated, and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (13 mg, 37% yield).

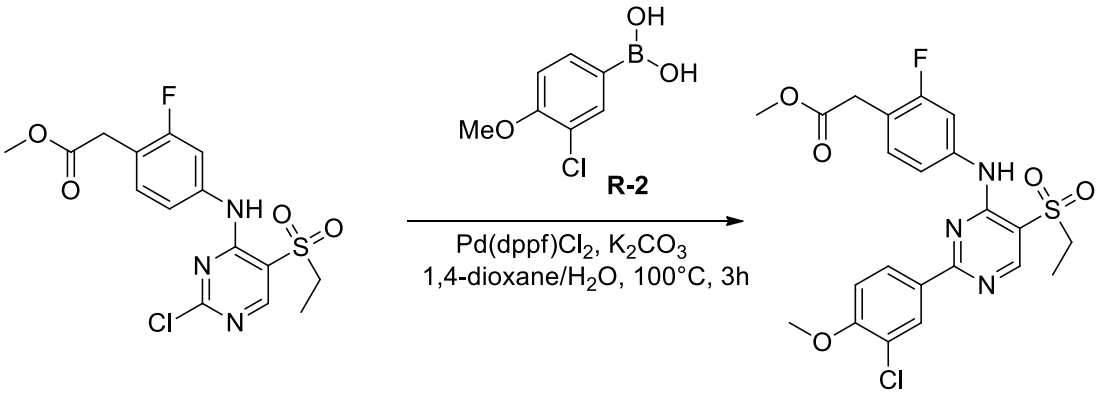
ESI-MS *m/z* calcd for [$C_{18}H_{18}ClN_5O_5S$] $[M+H]^+$: 452.1; found: 452.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.37 – 8.34 (m, 2H), 8.07 (s, 1H), 7.75 (s, 1H), 7.35 – 7.32 (m, 1H), 4.62 (s, 2H), 3.96 (s, 3H), 3.50 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).



MX02352

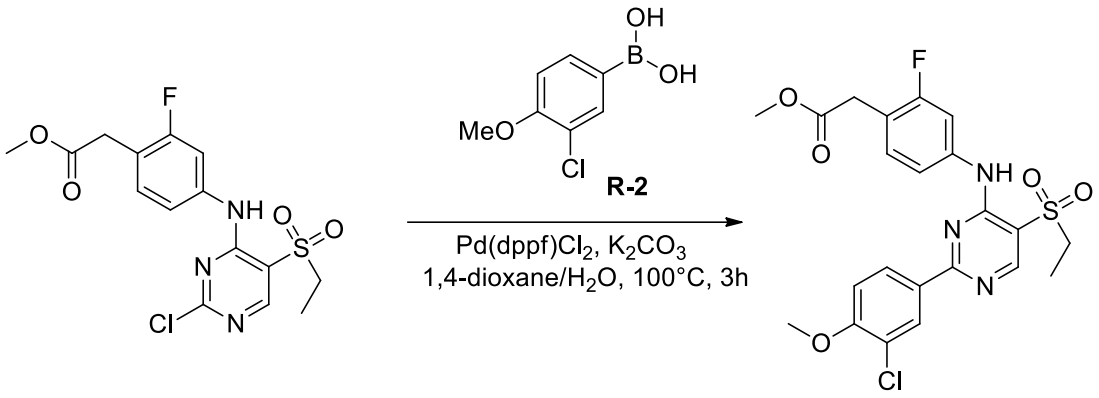
1. Synthetic scheme:



2. Experimental section:

2.1

(R)-2-((1H-indol-5-yl)ethynyl)-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02373)

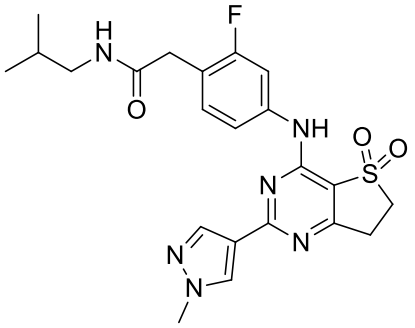


02161-4 **MX02352**

To a solution of methyl 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (25 mg, 0.065 mmol) in 1,4-dioxane/water (2.5 mL, v/v = 5/1) was added 3-chloro-4-methoxyphenylboronic acid (14.5 mg, 0.08 mmol), K_2CO_3 (27 mg, 0.195 mmol), and $Pd(dppf)Cl_2$ (5 mg, 0.006 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 3 hours until the starting material was consumed. Water (10 mL) was added, and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (15.0 mg, 47.1% yield).

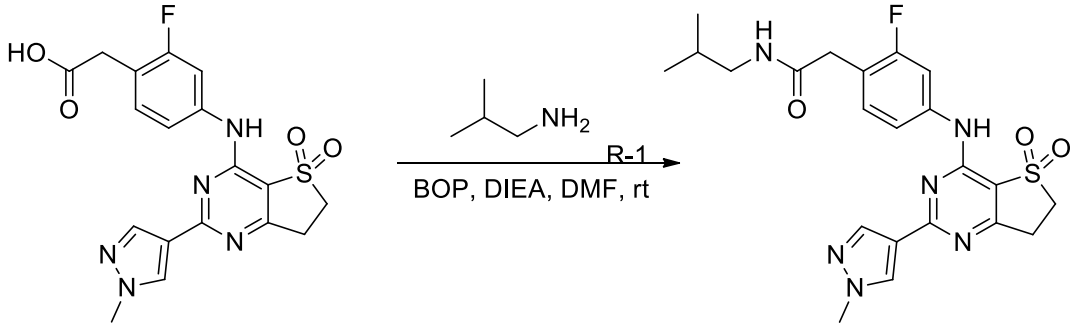
ESI-MS *m/z* calcd for $[C_{22}H_{21}ClFN_3O_5S]$ $[M+H]^+$: 494.1; found: 493.5

^1H NMR (400 MHz, DMSO-d_6) δ9.18 (s, 1H), 8.79 (s, 1H), 8.29 – 8.24 (m, 2H), 7.73 (d, J = 12.4 Hz, 1H), 7.42 – 7.40 (m, 2H), 7.35 (d, J = 8.8 Hz, 1H), 3.96 (s, 3H), 3.78 (s, 2H), 3.65 (s, 3H), 3.54 (q, J = 7.2 Hz,2H), 1.25 (t, J = 7.2 Hz, 3H).



MX02353

1. Synthetic scheme:

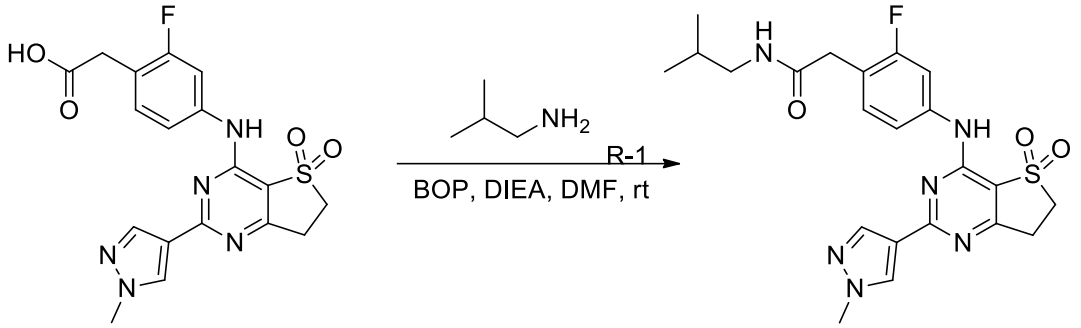


MX02315 **MX02353**

2. Experimental section:

2.1

2-(2-Fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)-N-isobutylacetamide(MX02353)

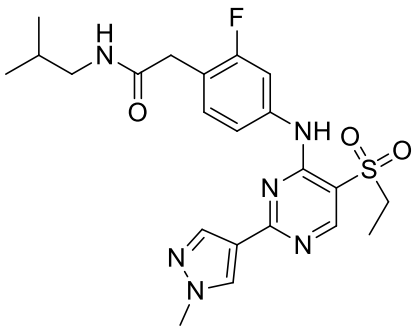


MX02315 **MX02353**

To a solution of 2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid (25 mg, 0.06 mmol) and isobutylamine (13.1 mg, 0.18 mmol) in DMF (3 mL) was added BOP (53 mg, 0.12 mmol) and DIEA (31 mg, 0.24 mmol). The mixture was stirred at room temperature for 16 hours. The mixture was filtered, and the filtrate was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (15.09 mg, 53.32% yield).

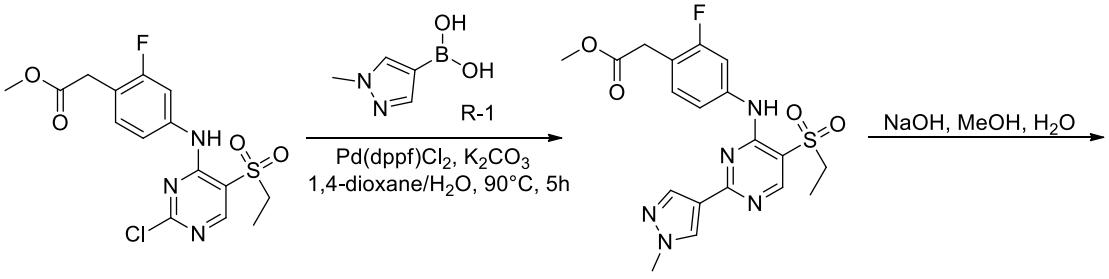
ESI-MS *m/z* calcd for $[C_{22}H_{25}FN_6O_3S]$ $[M+H]^+$:473.2; found:473.0

^{1}H NMR (400 MHz, Methanol-d_4) δ8.21 (s, 1H), 8.05 (s, 1H), 7.64 (dd, *J* = 12.0, 2.0 Hz, 1H), 7.46 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.64 (t, *J* = 6.8 Hz, 2H), 3.59 (s, 2H), 3.40 – 3.36 (m, 2H), 3.03 (d, *J* = 6.8 Hz, 2H), 1.84 – 1.77 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 6H).

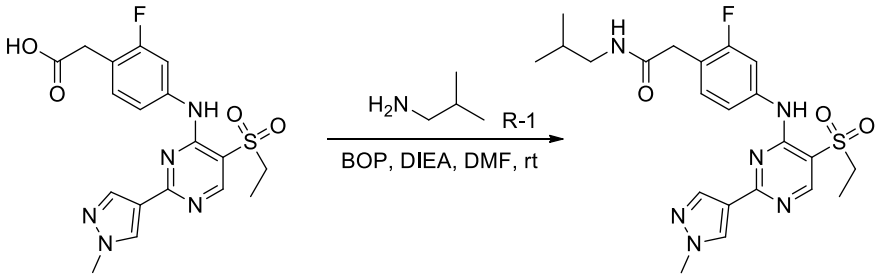


MX02354

1. Synthetic scheme:



02354-0 **02354-1**

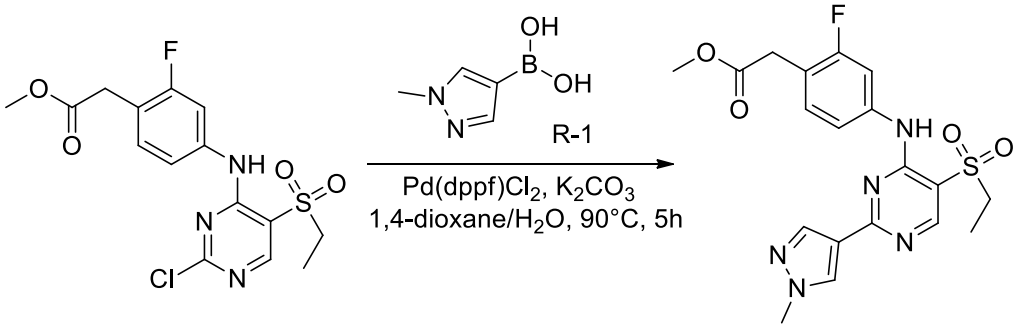


02354-2 **MX02354**

2. Experimental section:

2.1

Methyl2-(4-((5-(ethylsulfonyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate(02354-1)



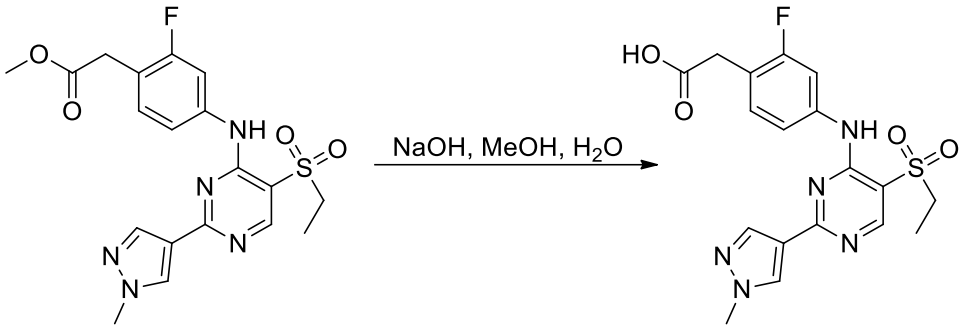
02354-0 **02354-1**

To a solution of methyl 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (40 mg, 0.1 mmol) in DMF (3 mL) was added 1-methyl-1H-pyrazol-4-ylboronic acid (19.5 mg, 0.16 mmol), K_2CO_3 (57 mg, 0.41 mmol), and $Pd(dppf)Cl_2$ (8.4 mg, 0.01 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C for 5 hours until the starting material was consumed. Water (20 mL) was added to quench the reaction mixture, and the mixture was extracted with EA (20 mL) twice. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (DCM/MeOH=0 to 10%, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (25 mg, 55.92% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{20}FN_5O_4S]$ $[M+H]^+$:434.1; found: 434.0

2.2

2-(4-((5-(Ethylsulfonyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid(02354-2)



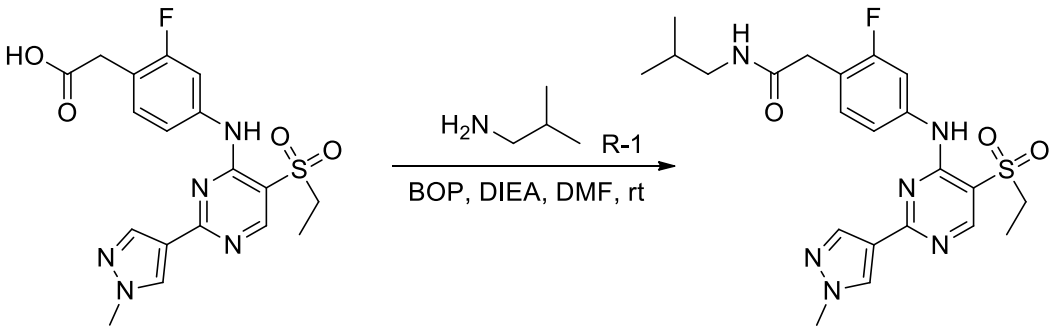
02354-1 **02354-2**

To a solution of methyl 2-(4-(((5-(ethylsulfonyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (25 mg, 0.058 mmol) in MeOH (3 mL) was added aqueous NaOH (11.5 mg, 0.29 mmol in 1 mL of water). The mixture was stirred at room temperature for 2 hours. The pH of the solution was adjusted to 6 with AcOH. The mixture was filtered, and the filtrate was purified by reverse-phase chromatography [MeCN/H_2O, C-18, 40 g, 45 mL/min, UV 254] to afford the yellow solid (15 mg, 62.01% yield).

ESI-MS *m/z* calcd for $[C_{18}H_{18}FN_5O_4S]$ $[M+H]^+$:420.1; found:420.0

2.3

2-(4-((5-(Ethylsulfonyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutylethanamide(MX02354)

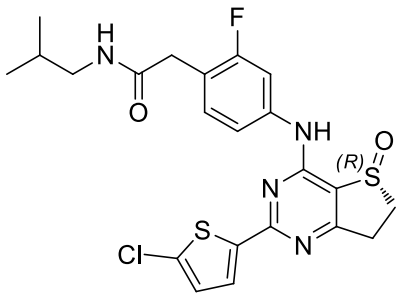


02354-2 **MX02354**

To a solution of 2-(4-((5-(ethylsulfonyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (15 mg, 0.036 mmol) and isobutylamine (7.8 mg, 0.11 mmol) in DMF (3 mL) was added BOP (31.6 mg, 0.072 mmol) and DIEA (18.5 mg, 0.14 mmol). The mixture was stirred at room temperature for 16 hours. The mixture was filtered, and the filtrate was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (2.31 mg, 9.85% yield).

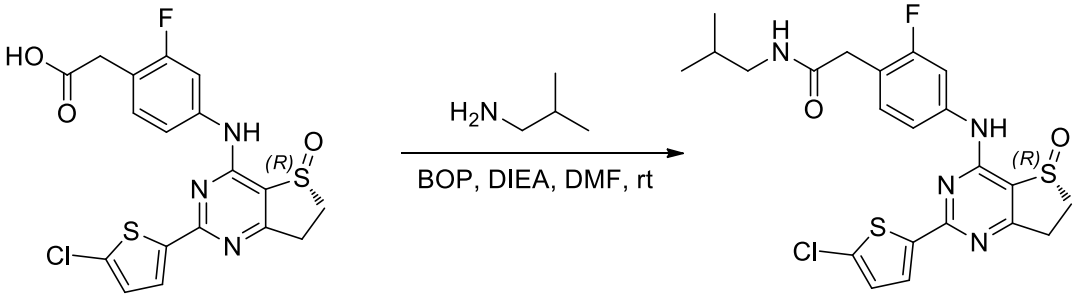
ESI-MS *m/z* calcd for $[C_{22}H_{27}FN_6O_3S]$ $[M+H]^+$:475.2; found:475.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 7.70 – 7.67 (m, 1H), 7.37 – 7.36 (m, 2H), 3.96 (s, 3H), 3.59 (s, 2H), 3.35 (q, *J* = 7.2 Hz, 2H), 3.03 (d, *J* = 6.8 Hz, 2H), 1.84 – 1.77 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 6H).



MX02355

1. Synthetic scheme:



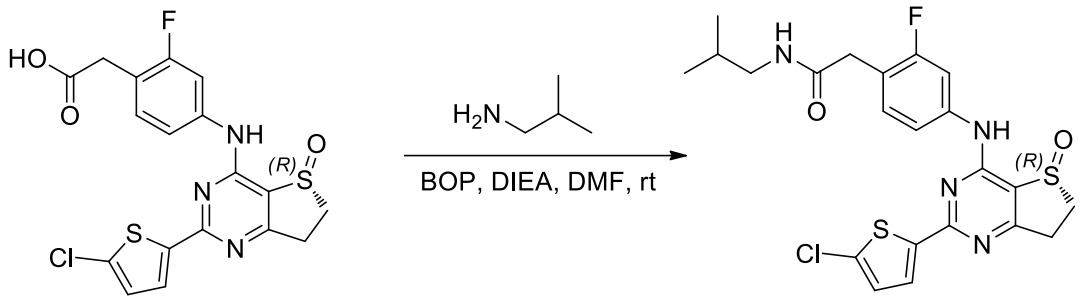
MX02159 **MX02355**

2. Experimental section:

2.1

(R)-2-(4-((2-(5-Chloro-2-thienyl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutylethanamide

(MX02355)

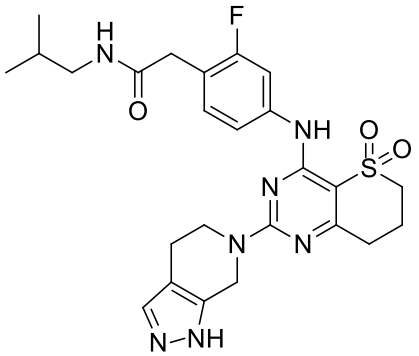


MX02159 **MX02355**

To a solution of (R)-2-(4-((2-(5-chlorothiophen-2-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (10 mg, 0.02 mmol) in DMF (3 mL) was added BOP (13.26 mg, 0.03 mmol), DIEA (7.74 mg, 0.06 mmol) and isobutylamine (2.32 mg, 0.02 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature for 2 hours until the starting material was consumed. The reaction mixture was concentrated in vacuo, and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (1.04 mg, 9.42% yield).

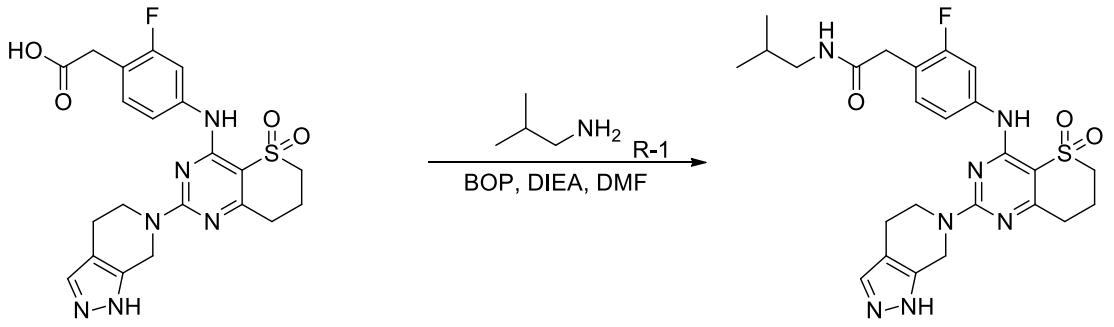
ESI-MS *m/z* calcd for $[C_{22}H_{22}ClFN_4O_2S_2]$ $[M+H]^+$: 493.1; found: 493.0

^1H NMR (400 MHz, DMSO-d_6) δ 10.15 (br, 1H), 8.06 (t, *J* = 5.2 Hz, 1H), 7.75 (d, *J* = 4.0 Hz, 1H), 7.65 (dd, *J* = 12.4, 2.0 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 4.0 Hz, 1H), 3.77 – 3.68 (m, 1H), 3.48 (s, 2H), 3.45 – 3.40 (m, 1H), 3.16 – 3.11 (m, 1H), 2.91 (t, *J* = 6.4 Hz, 2H), 1.73 – 1.67 (m, 1H), 0.88 – 0.84 (m, 7H).



MX02356

1. Synthetic scheme:

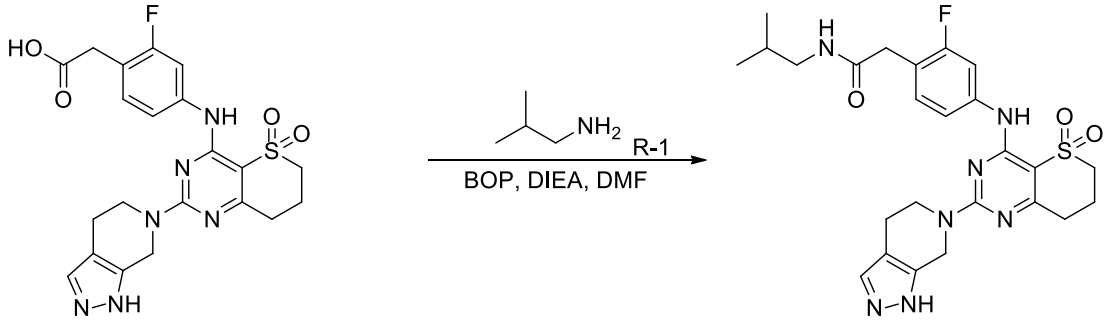


MX02170 **MX02356**

2. Experimental section:

2.1

2-(4-((2-(4,5-Dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5, 5-dioxo-7,8-dihydro-6H-thieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutylacetamide(MX02356)

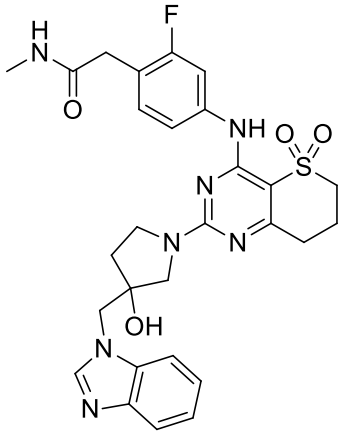


MX02170 **MX02356**

To a solution of 2-(4-((2-(4,5-dihydro-1H-pyrazolo[3,4-c]pyridin-6(7H)-yl)-5,5-dioxo-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (30 mg, 0.063 mmol) and isobutylamine (14 mg, 0.19 mmol) in DMF (3 mL) was added BOP (56.2 mg, 0.13 mmol) and DIEA (32.8 mg, 0.25 mmol). The mixture was stirred at room temperature for 16 hours. The mixture was filtered, and the filtrate was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (14.65 mg, 43.73% yield).

ESI-MS *m/z* calcd for $[C_{25}H_{30}FN_7O_3S]$ $[M+H]^+$:528.2; found:528.0

^{1}H NMR (400 MHz, Methanol-d_4) δ7.65 – 7.54 (m, 1H), 7.46 – 7.38 (m, 1H),7.34 – 7.28 (m, 1H), 7.24 – 7.20 (m, 1H), 5.04 – 4.89 (m, 2H), 4.08 – 4.02 (m, 2H), 3.53 (s,2H), 3.48 – 3.42 (m, 2H), 3.02 (d, J = 7.2 Hz, 2H), 2.89 (t, J = 6.4 Hz, 2H), 2.71 – 2.64 (m, 2H), 2.44 – 2.38 (m, 2H), 1.84 – 1.74 (m, 1H), 0.91 (d, J = 6.8Hz, 6H).



MX02357

1. Synthetic scheme:

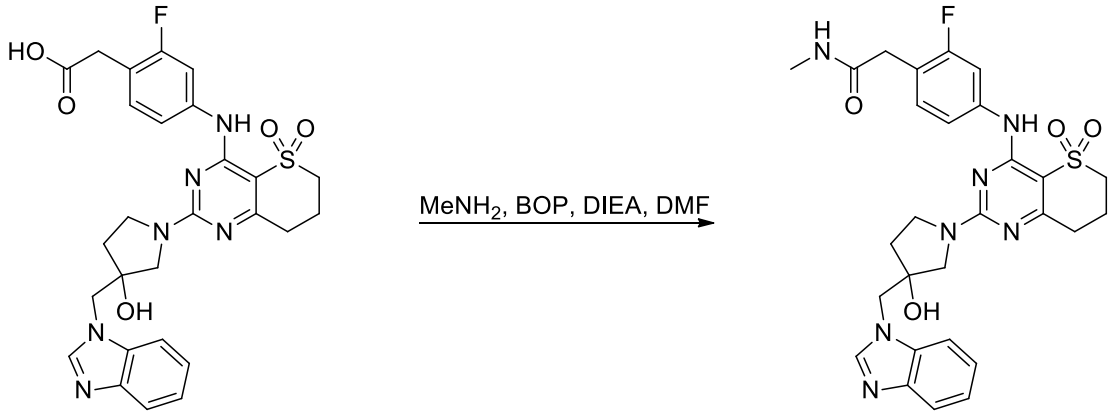


MX02288 **MX02357**

2. Experimental section:

2.1

2-(4-((2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-yl)-5, 5-dioxo-7,8-dihydro-6H-thieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-methylacetamide(MX02357)



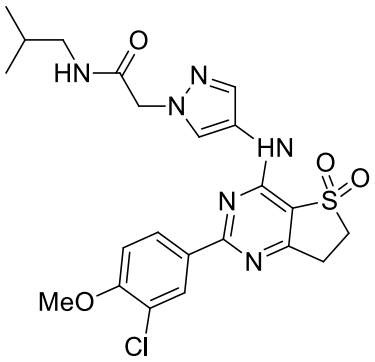
MX02288 **MX02357**

To a solution of 2-(4-((2-(3-((1H-benzo[d]imidazol-1-yl)methyl)-3-hydroxypyrrolidin-1-

yl)-5,5-dioxo-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (26 mg, 0.05 mmol) in DMF (3 mL) was added BOP (29.60 mg, 0.07 mmol), DIEA (17.40 mg, 0.14 mmol) and dimethylamine (2M THF solution) (0.07 mL, 0.14 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature for 2 hours until the starting material was consumed. The reaction mixture was concentrated in vacuo, and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (11.22 mg, 43.0% yield).

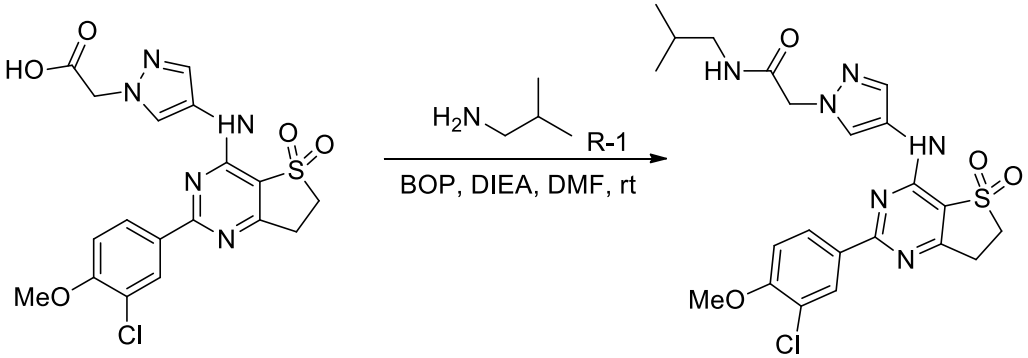
ESI-MS *m/z* calcd for $[C_{28}H_{30}FN_7O_4S]$ $[M+H]^+$: 580.2; found: 580.2

^{1}H NMR (400 MHz, DMSO-d_6) 8.68 (d, J = 12.0 Hz, 1H), 8.19 (d, J = 12.0 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.79 – 7.54 (m, 3H), 7.27 – 7.08 (m, 4H), 5.40 (d, J = 4.0 Hz, 1H), 4.51 – 4.42 (m, 2H), 3.74 – 3.41 (m, 8H), 2.81 (t, J = 6.4 Hz, 1H), 2.75 (t, J = 6.8 Hz, 1H), 2.68 – 2.55 (m, 3H), 2.30 – 2.23 (m, 2H), 2.14 – 2.06 (m, 1H), 1.89 – 1.75 (m, 1H).



MX02360

1. Synthetic scheme:

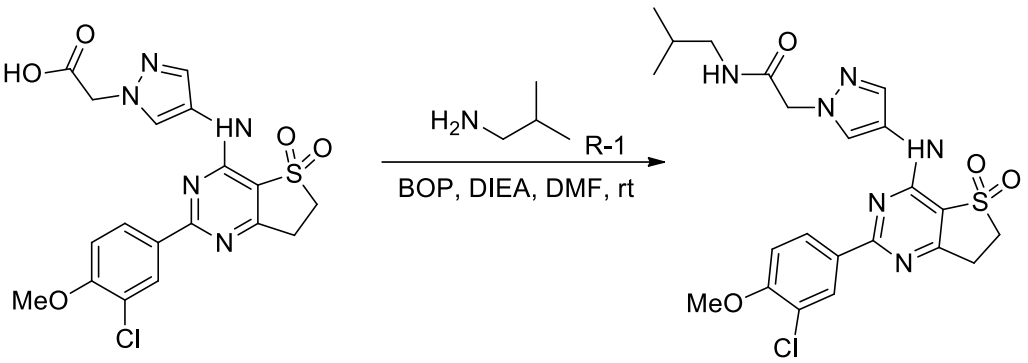


MX02349 **MX02360**

2. Experimental section:

2.1

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)-N-isobutylethanamide(MX02360)

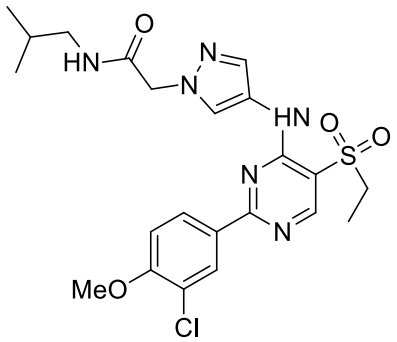


MX02349 **MX02360**

To a solution of 2-(4-((2-(3-chloro-4-methoxyphenyl)-5,5-dioxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetic acid (15 mg, 0.033 mmol) and isobutylamine (7.3 mg, 0.10 mmol) in DMF (2.5 mL) was added BOP (29.5 mg, 0.067 mmol) and DIEA (10.8 mg, 0.083 mmol). The mixture was filtered, and the filtrate was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (8.99 mg, 53.39% yield).

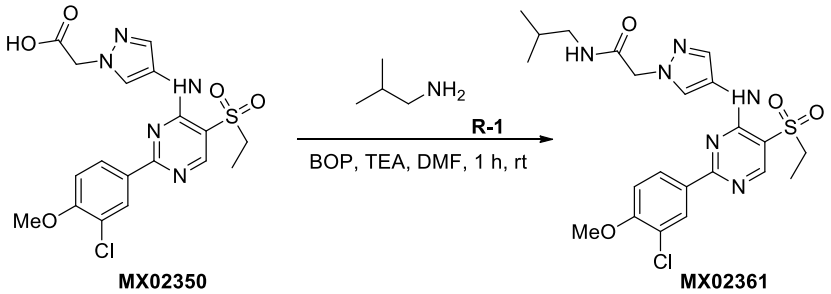
ESI-MS *m/z* calcd for [$C_{22}H_{25}ClN_6O_4S$] $[M+H]^+$:505.1; found:505.0

^{1}H NMR (400 MHz, Methanol-d_4) δ8.40 (d, J = 1.6 Hz, 1H), 8.37 – 8.34 (m, 1H), 8.18 (s, 1H), 7.87 (s, 1H), 7.20 (d, J = 8.4Hz, 1H), 4.91 (s, 2H), 3.98 (s, 3H), 3.60 (t, J = 6.4 Hz, 2H), 3.40 – 3.35 (m, 2H), 3.07 (d, J = 7.2 Hz, 2H), 1.83 – 1.78 (m, 1H), 0.92 (d, J = 6.8Hz, 6H).



MX02361

1. Synthetic scheme:

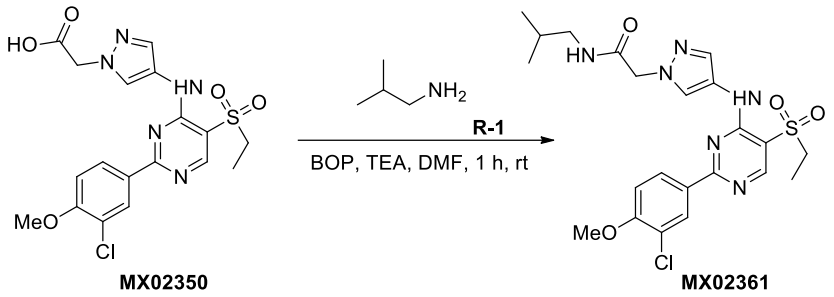


MX02350 **MX02361**

2. Experimental section:

2.1

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)-N-isobutylethanamide(MX02361)

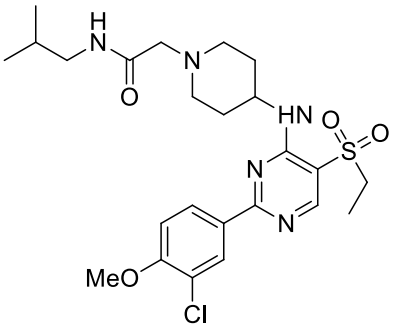


MX02350 MX02361

To a solution of 2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-1H-pyrazol-1-yl)acetic acid (6 mg, 0.01 mmol) and isobutylamine (1 mg, 0.012 mmol) in DMF (1 mL) was added BOP (7 mg, 0.015 mmol) and TEA (4 mg, 0.04 mmol). The mixture was stirred at room temperature for 1 hour and the reaction mixture was then filtered. The filtrate was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (2.13 mg, 32% yield).

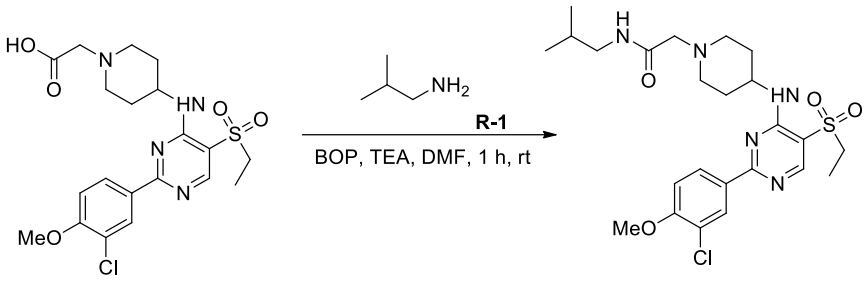
ESI-MS *m/z* calcd for [$C_{22}H_{27}ClN_6O_4S$] $[M+H]^+$:507.2; found:507.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.68 (s, 1H), 8.37 – 8.35 (m, 2H), 8.14 – 8.12 (m, 2H), 7.84 (s, 1H), 7.32 (d, J = 9.6 Hz, 1H), 4.85 (s, 2H), 3.96 (s, 3H), 3.50 (q, J = 7.2 Hz, 2H), 2.95 (t, J = 6.4 Hz, 2H), 1.77 – 1.67 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H), 0.86 (d, J = 6.8 Hz, 6H).



MX02363

1. Synthetic scheme:

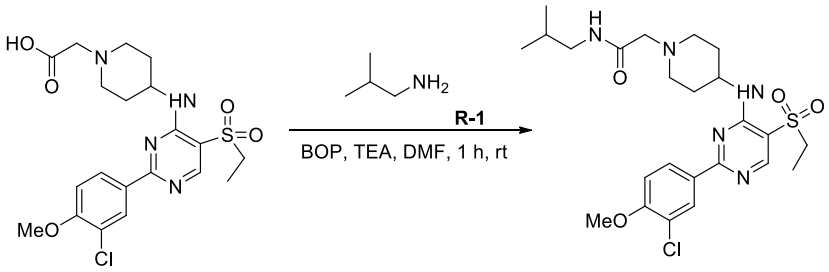


MX02347 **MX02363**

2. Experimental section:

2.1

2-(4-((2-(3-Chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)piperidin-1-yl)-N-isobutylethanamide (MX02363)

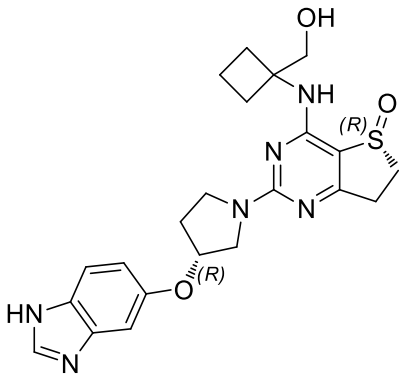


MX02347 **MX02363**

To a solution of 2-(4-((2-(3-chloro-4-methoxyphenyl)-5-(ethylsulfonyl)pyrimidin-4-yl)amino)piperidin-1-yl)acetic acid (5 mg, 0.01 mmol) and isobutylamine (1 mg, 0.012 mmol) in DMF (1 mL) was added BOP (7 mg, 0.015 mmol) and TEA (4 mg, 0.04 mmol). The mixture was stirred at room temperature for 1 hour and the reaction mixture was then filtered. The filtrate was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (2.98 mg, 53% yield).

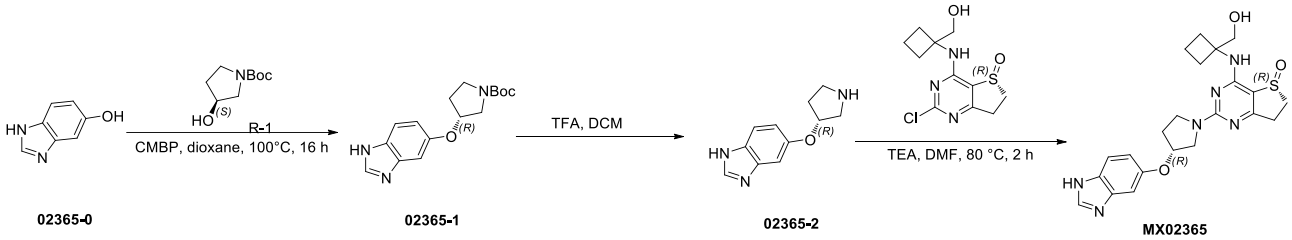
ESI-MS *m/z* calcd for [$C_{24}H_{34}ClN_5O_4S$] $[M+H]^+$:524.2; found:523.8

^{1}H NMR (400 MHz, Methanol-d_4) δ8.80 – 8.73 (m, 1H), 7.69 (s, 1H), 7.62 (dd, J = 8.8, 2.4 Hz, 1H), 7.16 (t, J = 6.8 Hz, 1H), 4.01 – 3.90 (m, 4H), 3.14 – 3.02 (m, 4H), 2.92 – 2.86 (m, 2H), 2.77 (q, J = 7.2 Hz, 2H), 2.37 – 2.27 (m, 2H), 2.06 – 1.97 (m, 2H), 1.83 – 1.65 (m, 3H), 1.06 (t, J = 7.6 Hz, 3H),0.92 (d, J = 6.8 Hz, 6H).



MX02365

1. Synthetic scheme:

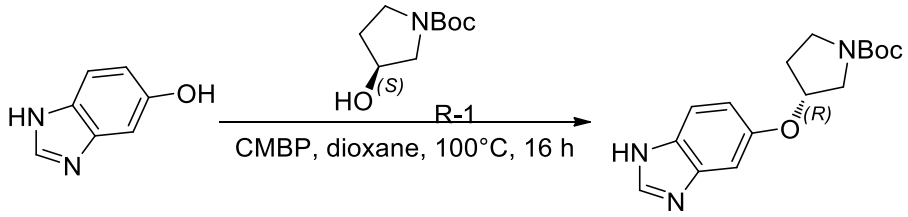


02365-0 **02365-1** **02365-2** **MX02365**

2. Experimental section:

2.1

(R)-3-((1H-benzo[d]imidazol-5-yl)oxy)pyrrolidine-1-carboxylic acid tert-butyl ester(02365-1)



02365-0 **02365-1**

To a solution of 5-hydroxy-1H-benzo[d]imidazole (250 mg, 1.86 mmol) and tert-butyl 3-hydroxypyrrolidine-1-carboxylate (419 mg, 2.24 mmol) in 1,4-dioxane (20 mL) was added CMBP (0.9 g, 3.73 mmol). The mixture was stirred at 100 °C for 16 hours, cooled to room temperature and concentrated. The crude product was purified by column chromatography (EA/PE=0 to 50%, silica gel, 40 g, 50 mL/min, UV 254) to afford the brown oil (481 mg, 85.08% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{21}N_3O_3]$ $[M+H]^+$:304.2; found:304.1

2.2

(R)-5-(Pyrrolidin-3-yloxy)-1H-benzo[d]imidazole(02365-2)



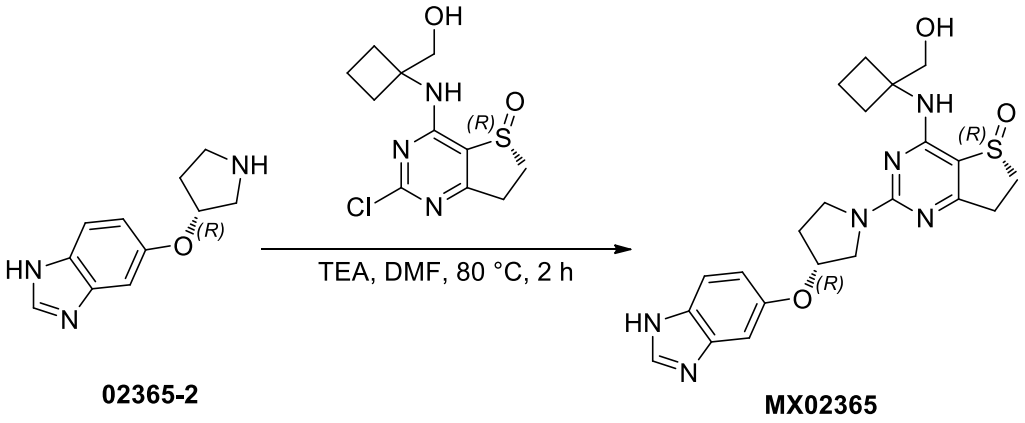
02365-1 **02365-2**

To a solution of (R)-3-((1H-benzo[d]imidazol-5-yl)oxy)pyrrolidine-1-carboxylic acid tert-butyl ester (66 mg, 0.22 mmol) in DCM (5 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 16 hours. The mixture was concentratedand the crude product was used directly for the next step.

ESI-MS *m/z* calcd for $[C_{11}H_{13}N_3O]$ $[M+H]^+$:204.1; found:204.2

2.3

(R)-2-((R)-3-((1H-benzo[d]imidazol-5-yl)oxy)pyrrolidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6, 7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02365)

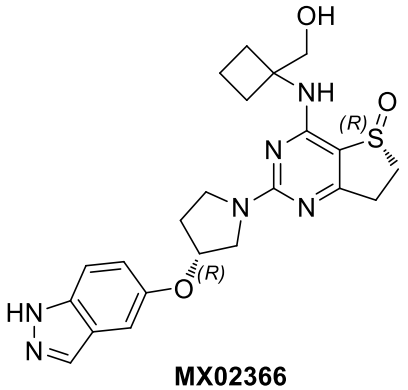


02365-2 **MX02365**

To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (40 mg, 0.14 mmol) and (R)-5-(pyrrolidin-3-yl oxy)-1H-benzo[d]imidazole (42.4 mg, 0.21 mmol) in DMF (3 mL) was added TEA (98.5 mg, 0.97 mmol). The mixture was stirred at 80 °C for 2 hours, cooled to room temperature and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (35.65 mg, 56.42% yield).

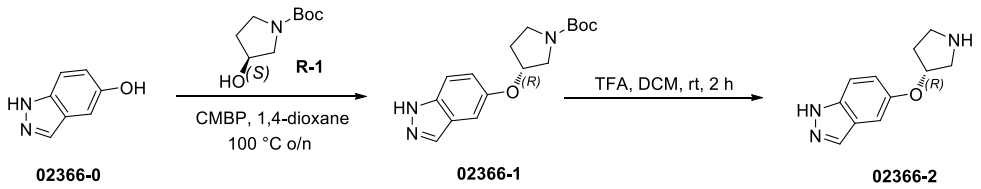
ESI-MS *m/z* calcd for $[C_{22}H_{26}N_6O_3S]$ $[M+H]^+$:455.2; found:455.0

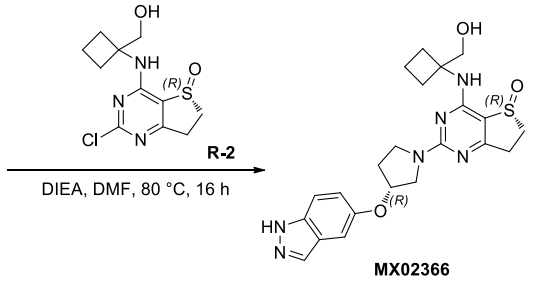
^{1}H NMR (400 MHz, Methanol-d_4) δ 8.08 (s, 1H), 7.50 -7.49 (m, 1H), 7.13 (s, 1H), 6.93 – 6.91 (m, 1H), 5.13 - 5.11 (m, 1H), 4.00 – 3.68 (m, 6H), 3.58 – 3.52 (m, 1H), 3.39 – 3.34 (m, 1H), 3.13 – 3.03 (m, 2H), 2.35 – 2.13 (m, 6H),1.93 – 1.76 (m, 2H).



MX02366

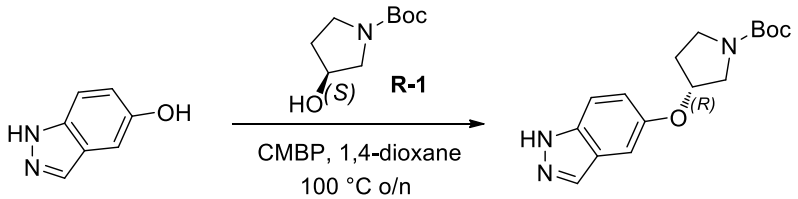
1. Synthetic scheme:





2. Experimental section:

2.1 (R)-3-((1H-Indazol-5-yl)oxy)pyrrolidine-1-carboxylic acid tert-butyl ester(02366-1)



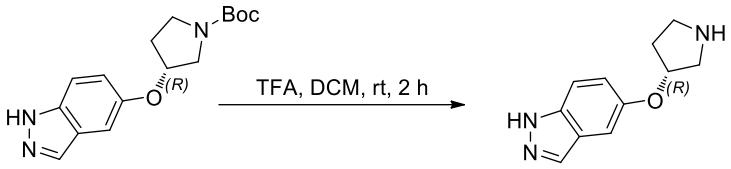
To a solution of 1H-indazol-5-ol (250 mg, 1.86 mmol) in 1,4-dioxane (10 mL) was added (S)-3-hydroxypyrrolidine-1-carboxylic acid tert-butyl ester (348 mg, 1.86 mmol) and CMBP (899 mg, 3.73 mmol). The mixture was stirred at 100 °C under a nitrogen atmosphere overnight. After cooling, water (30 mL) was added and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by

column chromatography (EA/PE=0/1 to 1/1, silica gel, 20 g, 30 mL/min, UV 254) to afford the yellow solid (550 mg, 97% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{21}N_3O_3]$ $[M+H]^+$: 304.2; found: 304.2

2.2

(R)-5-(Pyrrolidin-3-yloxy)-1H-indazole(02366-2)



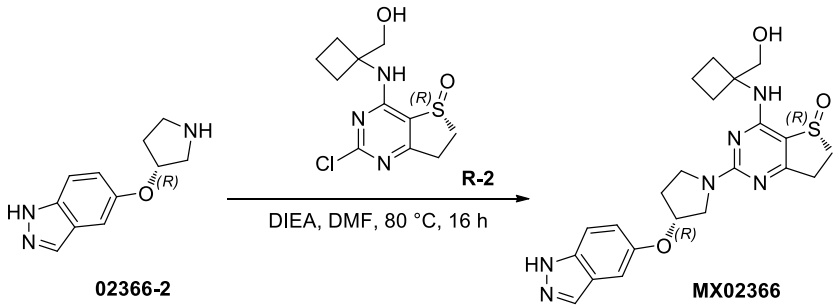
02366-1 02366-2

To a solution of (R)-3-((1H-indazol-5-yl)oxy)pyrrolidine-1-carboxylic acid tert-butyl ester (550 mg, 1.81 mmol) in DCM (10 mL) was added TFA (2 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours until the starting material was consumed, then concentrated in vacuo to afford the yellow oil (364 mg, 98% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{13}N_3O]$ $[M+H]^+$: 204.1; found: 204.3

2.3

(R)-2-((R)-3-((1H-indazol-5-yl)oxy)pyrrolidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02366)

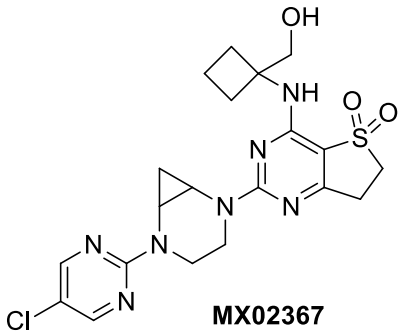


02366-2 MX02366

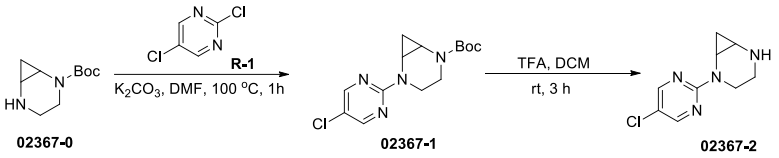
To a solution of (R)-5-(pyrrolidin-3-yl oxy)-1H-indazole (50 mg, 0.25 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (70 mg, 0.25 mmol) in DMF (3 mL) was added DIEA (97 mg, 0.75 mmol). The mixture was stirred under a nitrogen atmosphere at 80 °C for 16 hours until the starting material was consumed. After cooling, water (10 mL) was added, and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (25.47 mg, 23% yield).

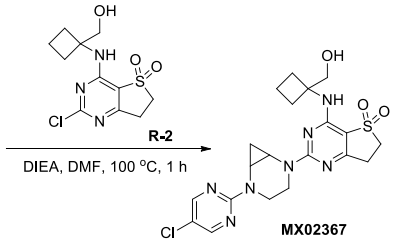
ESI-MS *m/z* calcd for $[C_{22}H_{26}N_6O_3S]$ $[M+H]^+$: 455.2; found: 454.9

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 7.95 (s, 1H), 7.44 (d, J = 9.2 Hz, 1H), 7.36– 7.25 (m, 2H), 7.00 (dd, J = 8.8, 2.0 Hz, 1H), 5.10 (s, 1H), 4.89 – 4.84 (m, 1H), 3.81 – 3.67 (m, 5H), 3.60 – 3.56 (m, 1H), 3.46 – 3.36 (m, 1H), 3.25 – 3.15 (m, 1H), 2.98 – 2.81 (m, 2H), 2.44 – 2.06 (m, 6H), 1.81 – 1.63 (m, 2H).



1. Synthetic scheme:

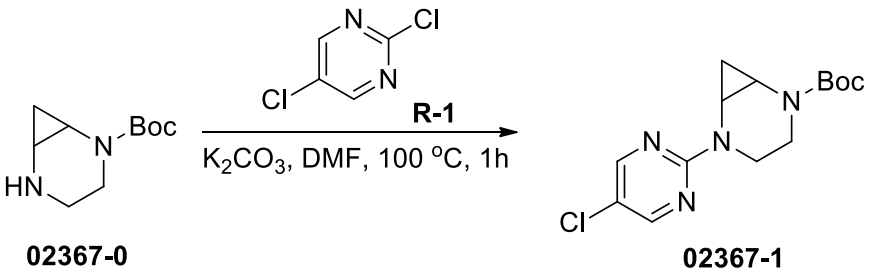




2. Experimental section:

2.1

5-(5-Chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylic acid tert-butyl ester(02367-1)

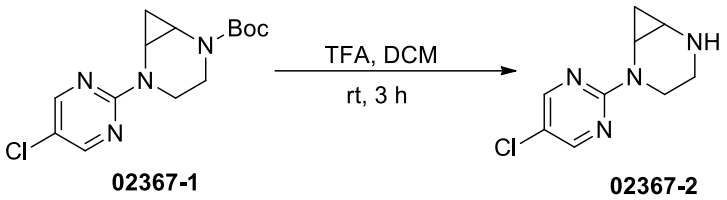


To a solution of 2,5-diazabicyclo[4.1.0]heptane-2-carboxylic acid tert-butyl ester (100 mg, 0.51 mmol) in DMF (3 mL) was added 2,5-dichloropyrimidine (76 mg, 0.51 mmol) and K_2CO_3 (211 mg, 1.53 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 1 hour. Water (20 mL) was added and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0/1 to 1/1, silica gel, 20 g, 30 mL/min, UV 254) to afford the white solid (140 mg, 90% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{19}ClN_4O_2]$ $[M-56+H]^+$: 255.1; found: 255.2

2.2

2-(5-Chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane(02367-2)



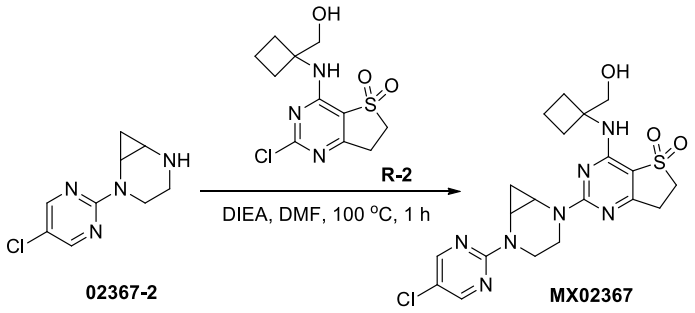
02367-1 02367-2

To a solution of 5-(5-chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-carboxylic acid tert-butyl ester (140 mg, 0.45 mmol) in DCM (5 mL) was added TFA (0.5 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 3 hours until the starting material was consumed. The mixture was concentrated in vacuo to afford the white solid (90 mg, 95% yield).

ESI-MS *m/z* calcd for $[C_9H_{11}ClN_4]$ $[M+H]^+$: 211.1; found: 211.3

2.3

2-(5-(5-Chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane-2-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine heptan-2-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5,5-dioxide(MX02367)



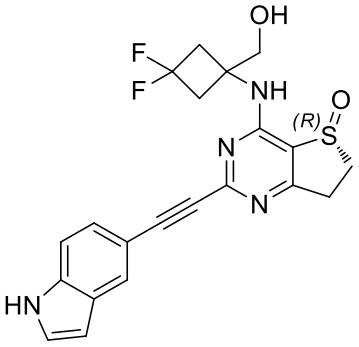
02367-2 MX02367

To a solution of 2-(5-chloropyrimidin-2-yl)-2,5-diazabicyclo[4.1.0]heptane (15 mg, 0.07 mmol) in DMF (2 mL) was added 2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-

dihydrothieno[3,2-d]pyrimidine 5,5-dioxide (21 mg, 0.07 mmol) and DIEA (27 mg, 0.21 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 1 hour until the starting material was consumed. After cooling, water (10 mL) was added, and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (18.94 mg, 56% yield).

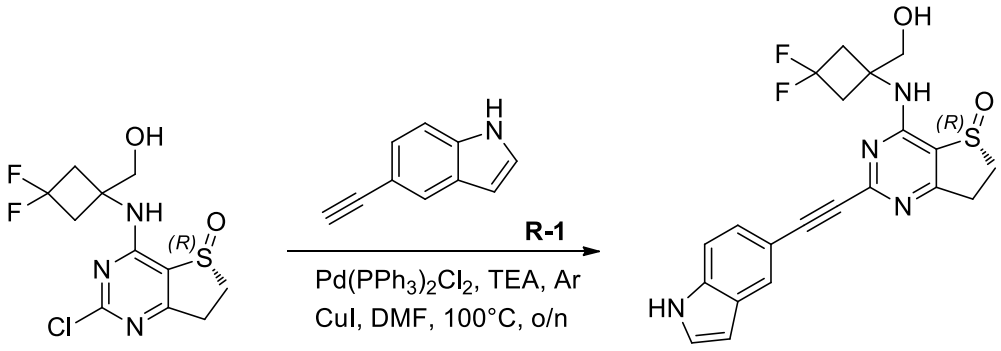
ESI-MS *m/z* calcd for $[C_{20}H_{24}ClN_7O_3S]$ $[M+H]^+$: 478.1; found: 478.2

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 2H), 6.18– 6.16 (m, 1H), 5.02 (t, J = 5.2 Hz, 1H), 4.05 – 3.84 (m, 1H), 3.84 – 3.68 (m, 4H), 3.58 – 3.42 (m, 4H), 3.37 – 3.30 (m, 1H), 3.13 – 3.07 (m, 2H), 2.67 – 2.56 (m, 2H), 2.11 – 2.08 (m, 2H), 1.87 – 1.70 (m, 2H), 1.22 – 1.14 (m, 1H), 0.48 – 0.42 (m, 1H).



MX02373

1. Synthetic scheme:

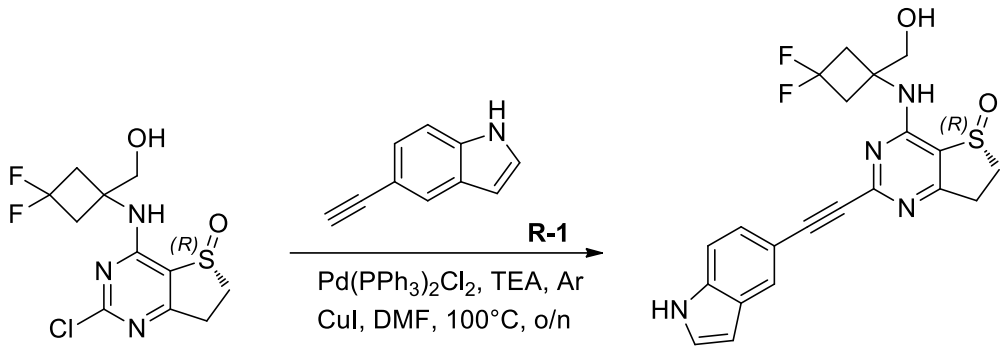


02373-0 **MX02373**

2. Experimental section:

2.1

(R)-2-((1H-indol-5-yl)ethynyl)-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02373)

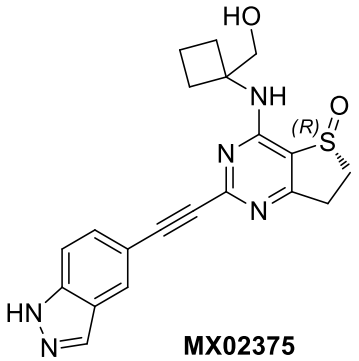


02371-2 **MX02373**

To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)-3,3-difluorocyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (20 mg, 0.062 mmol) in DMF (5 mL) was added 5-ethynyl-1H-indole (10.5 mg, 0.074 mmol), CuI (1.3 mg, 0.006 mmol), TEA (14.3 mg, 0.142 mmol) and $Pd(PPh_3)_2Cl_2$ (4.5 mg, 0.006 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C overnight until the starting material was consumed. Water (10 mL) was added to quench the reaction, and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (8.0 mg, 30.3% yield).

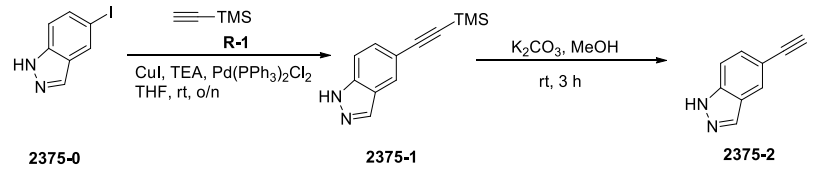
ESI-MS *m/z* calcd for $[C_{21}H_{18}F_2N_4O_2S]$ $[M+H]^+$: 429.1; found: 428.9

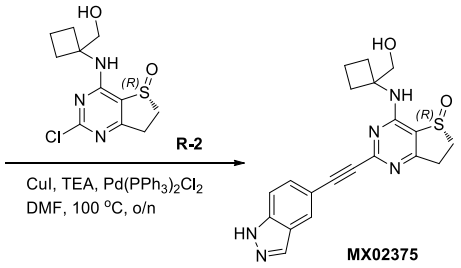
^1H NMR (400 MHz, DMSO-d_6) δ11.45 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.48 – 7.46 (m, 2H), 7.31 (dd, J = 8.4，1.6 Hz, 1H), 6.51 (d, J = 2.4，1H), 5.24 (t, J = 5.6 Hz, 1H), 3.74 – 3.71 (m, 2H), 3.64 – 3.57 (m, 1H), 3.37 – 3.35 (m, 1H), 3.22 – 3.16 (m, 1H), 3.07 – 2.91 (m, 5H).



MX02375

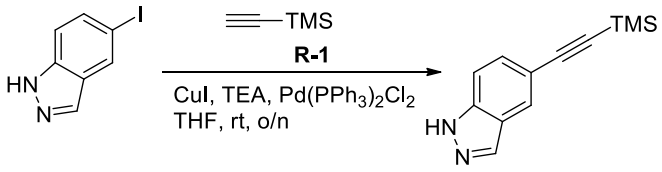
1. Synthetic scheme:





2. Experimental section:

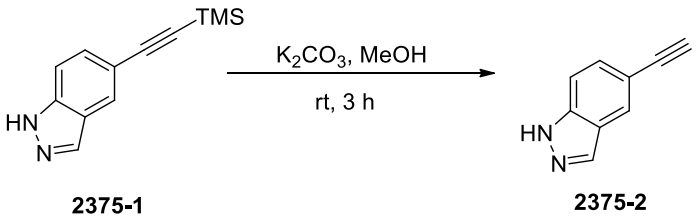
2.1 5-((Trimethylsilyl)ethynyl)-1H-indazole(02375-1)



To a solution of 5-iodo-1H-indazole (1 g, 4.11 mmol) in THF (10 mL) was added trimethylsilylacetylene (444 mg, 4.53 mmol), CuI (78 mg, 0.41 mmol), TEA (5 mL) and $Pd(PPh_3)_2Cl_2$ (84 mg, 0.12 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature overnight until the starting material was consumed. The reaction mixture was concentrated in vacuo and the crude product was purified by column chromatography (EA/PE=0/1 to 1/10, silica gel, 40 g, 40 mL/min, UV 254) to afford the brown solid (670 mg, 76% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{14}N_2Si]$ $[M+H]^+$: 215.1; found: 215.4

2.2 5-Ethynyl-1H-indazole(02375-2)



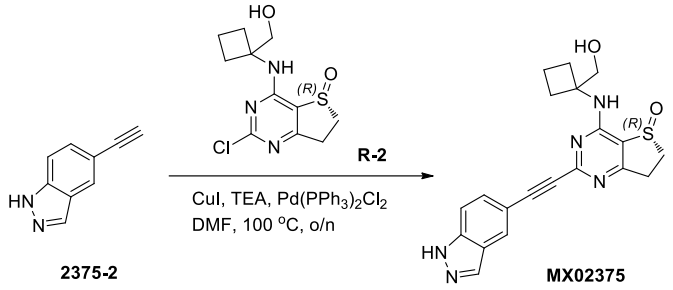
To a solution of 5-((trimethylsilyl)ethynyl)-1H-indazole (670 mg, 3.13 mmol) in MeOH (10 mL) was added K_2CO_3 (648 mg, 4.69 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature for 3 hours until the starting material was consumed. The reaction mixture was filtered and concentrated to afford the brown solid (440 mg, 95% yield),

which was used directly for the next step.

ESI-MS *m/z* calcd for $[C_9H_6N_2]$ $[M+H]^+$: 143.1; found: 143.4

2.3

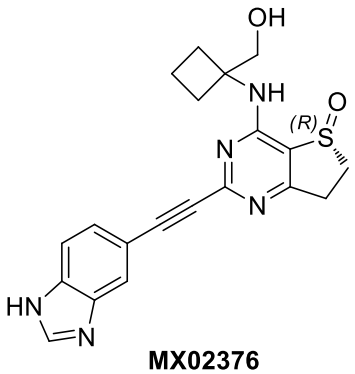
(R)-2-((1H-Indazol-5-yl)ethynyl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02375)



To a solution of 5-ethynyl-1H-indazole (50 mg, 0.36 mmol) in DMF (3 mL) was added (R)-2-chloro-4-[(1-(hydroxymethyl)cyclobutyl)amino]-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (102 mg, 0.36 mmol), CuI (6 mg, 0.035 mmol), TEA (71 mg, 0.71 mmol) and $Pd(PPh_3)_2Cl_2$ (17 mg, 0.025 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C overnight until the starting material was consumed. Water (20 mL) was added to quench the reaction and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (2.12 mg, 2% yield).

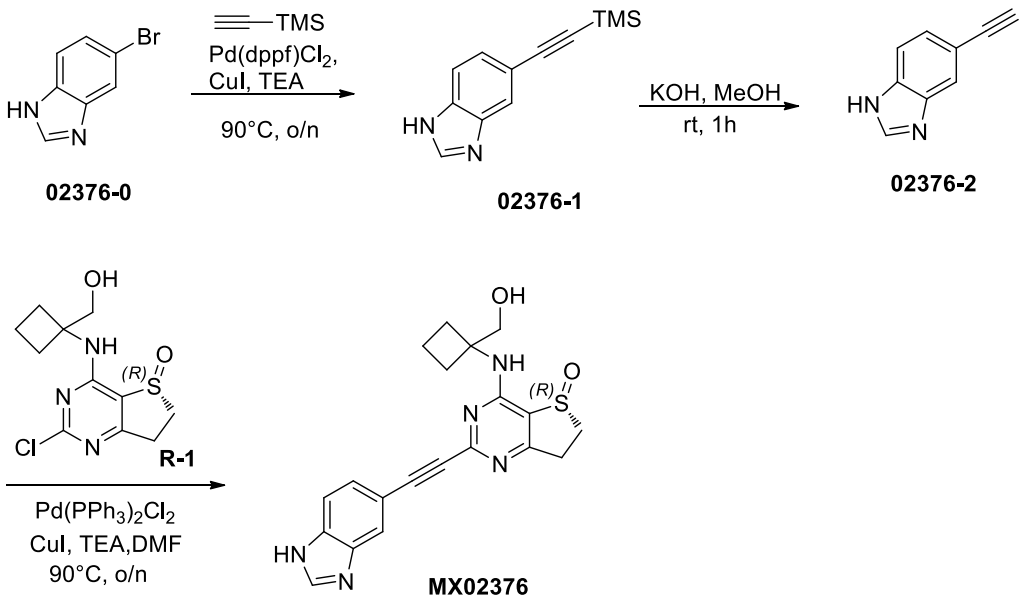
ESI-MS *m/z* calcd for $[C_{20}H_{19}N_5O_2S]$ $[M+H]^+$: 394.1; found: 394.2

^{1}H NMR (400 MHz, DMSO-d_6) δ13.38 (s, 1H), 8.18 – 8.15 (m, 2H), 8.13 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.52 (dd, J = 8.8, 1.2 Hz, 1H), 4.92 (t, J = 5.6 Hz, 1H), 3.78 – 3.72 (m, 2H), 3.62 – 3.54 (m, 1H), 3.39 – 3.37 (m, 1H), 3.19 – 3.13 (m, 1H), 3.05 – 3.00 (m, 1H), 2.38 – 2.24 (m, 4H), 1.85 – 1.74 (m, 2H).



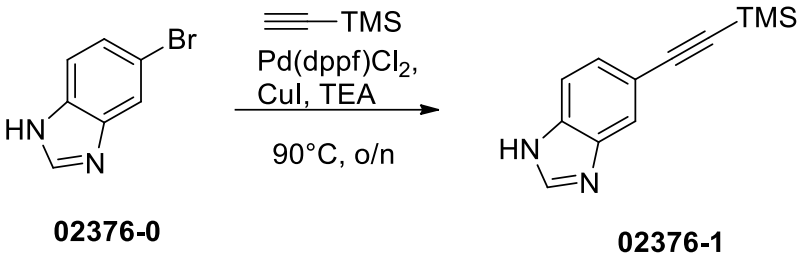
MX02376

1. Synthetic scheme:



2. Experimental section:

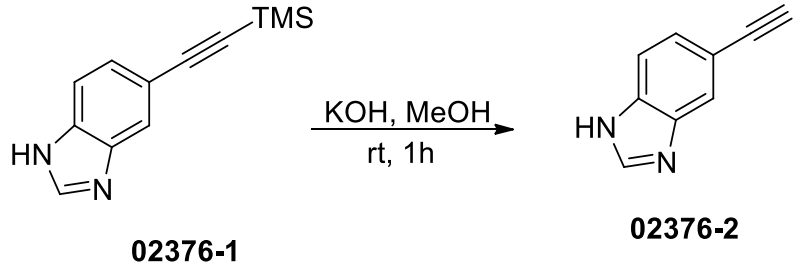
2.1 5-((Trimethylsilyl)ethynyl)-1H-benzo[d]imidazole(02376-1)



To a solution of 5-bromo-1H-benzo[d]imidazole (1 g, 5.08 mmol), $Pd(dppf)Cl_2$ (186 mg, 0.254 mmol) and CuI (97 mg, 0.51 mmol) in DMF (5 mL) was added TEA (5 mL) and trimethylsilylacetylene (1 g, 10.16 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C overnight. The solvent was removed in vacuo and the crude product was purified by column chromatography (MeOH/DCM=0/1 to 1/10, silica gel, 20 g, 40 mL/min, UV 254) to afford the yellow solid (550 mg, 50.6% yield).

ESI-MS m/z calcd for [C12H14N2Si] [M+H]+: 215.1; found: 215.2

2.2 5-Ethynyl-1H-benzo[d]imidazole(02376-2)



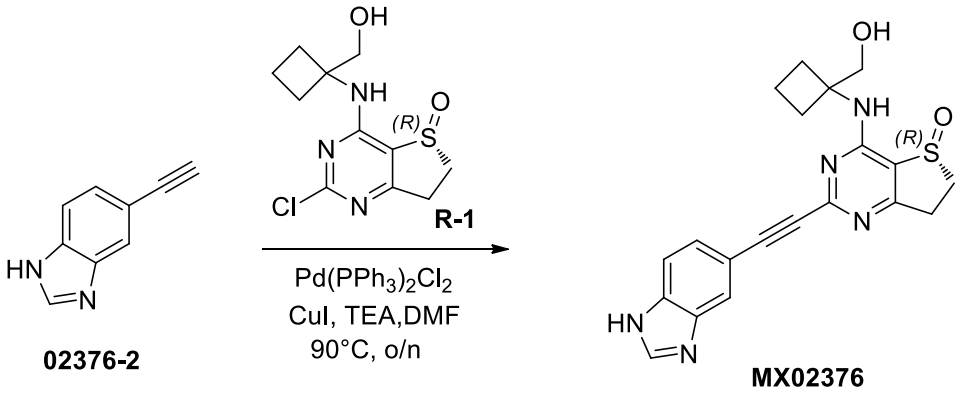
To a solution of 5-((trimethylsilyl)ethynyl)-1H-benzo[d]imidazole (550 mg, 2.57 mmol) in MeOH (10 mL) was added KOH (289 mg, 5.14 mmol). The mixture was stirred at room

temperature for 1 hour. The pH of the mixture was adjusted to 6 with 1N HCl aqueous solution, and the solvent was removed in vacuo. The crude product was purified by column chromatography (MeOH/DCM=0/1 to 1/10, silica gel, 20 g, 40 mL/min, UV 254) to afford the yellow solid (148 mg, 40.6% yield).

ESI-MS *m/z* calcd for $[C_9H_6N_2]$ $[M+H]^+$: 143.1; found: 143.3.

2.3

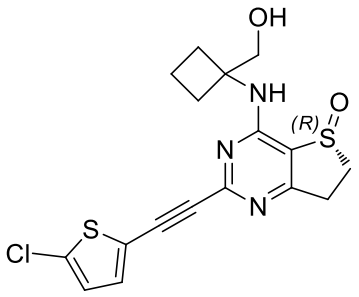
(R)-2-((1H-benzo[d]imidazol-5-yl)ethynyl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02376)



To a solution of 5-ethynyl-1H-benzo[d]imidazole (73 mg, 0.514 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (148 mg, 0.514 mmol) in DMF (4 mL) was added TEA (156 mg, 1.542 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) and CuI (10 mg, 0.05 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C overnight. The solvent was removed in vacuo and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (15 mg, 7.43% yield).

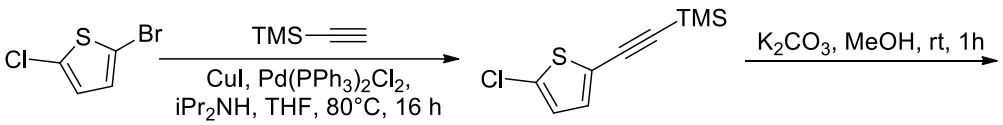
ESI-MS *m/z* calcd for $[C_{20}H_{19}N_5O_2S]$ $[M+H]^+$: 394.1; found: 394.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 8.36 (s, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 7.67 – 7.65 (m, 1H), 7.42 (d, J = 8.0 Hz, 1H), 4.92 (t, J = 5.6 Hz, 1H), 3.80 – 3.72 (m, 2H), 3.62 – 3.54 (m, 1H), 3.39 – 3.34 (m, 1H), 3.20 – 3.13 (m, 1H), 3.05 – 2.99 (m, 1H), 2.38 – 2.25 (m, 4H), 1.84 – 1.76 (m, 2H).

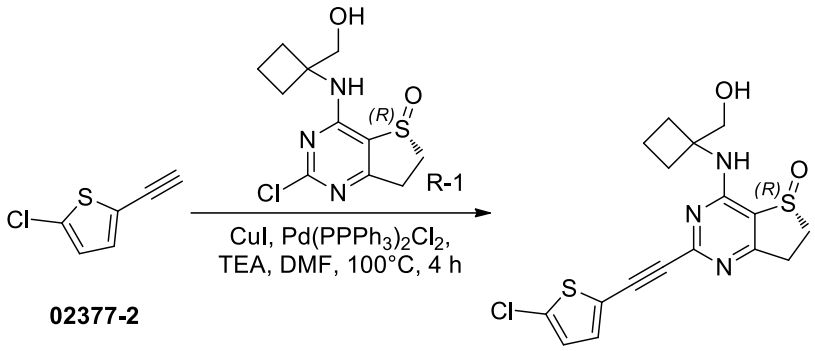


MX02377

1. Synthetic scheme:



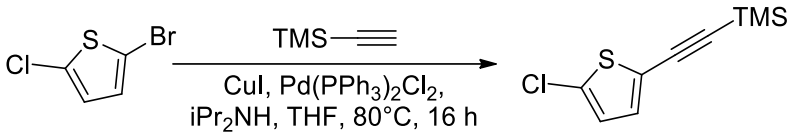
02377-0 **02377-1**



02377-2 **MX02377**

2. Experimental section:

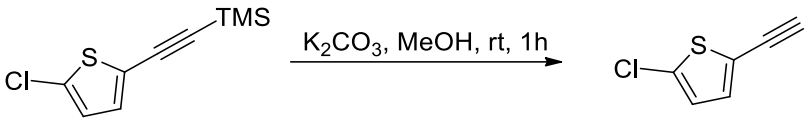
2.1 (5-Chlorothiophen-2-yl)ethynyltrimethylsilane(02377-1)



02377-0 **02377-1**

To a solution of 2-bromo-5-chlorothiophene (2 g, 10.13 mmol) in THF (50 mL) was added trimethylsilylacetylene (2.98 g, 30.38 mmol), CuI (96 mg, 0.51 mmol), $Pd(PPh_3)_2Cl_2$ (355 mg, 0.51 mmol), and diisopropylamine (2.05 g, 20.26 mmol). The mixture was stirred under a nitrogen atmosphere at 80 °C for 16 hours, cooled to room temperature, and concentrated. The crude product was purified by column chromatography (EA/PE, 0 to 2%, silica gel, 40 g, 50 mL/min, UV 254) to afford the yellow oil (1.2 g, 55.16% yield).

2.2 2-Chloro-5-ethynylthiophene(02377-2)



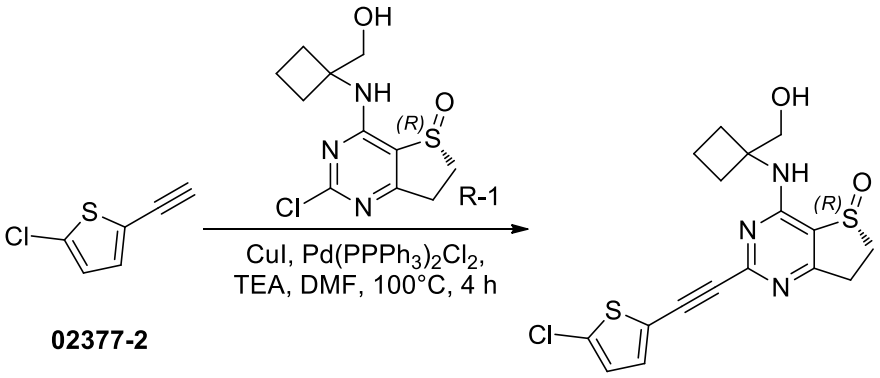
02377-1 **02377-2**

To a solution of (5-chlorothiophen-2-yl)ethynyl)trimethylsilane (1.2 g, 5.59 mmol) in MeOH (50 mL) was added K_2CO_3 (1.54 g, 11.17 mmol). The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography (EA/PE, 0 to 25%, silica gel, 20 g, 25 mL/min, UV 254) to afford the brown solid (0.7 g, 87.86% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ7.05 (d, *J* = 4.0 Hz, 1H), 6.79 (d, *J* = 3.6 Hz,1H), 3.33(s, 1H).

2.3

(R)-2-((5-Chlorothien-2-yl)ethynyl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02377)

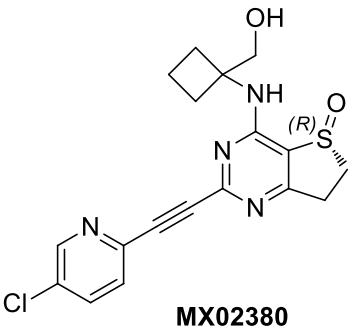


02377-2 **MX02377**

To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (66 mg, 0.23 mmol) and 2-chloro-5-ethynylthiophene (98 mg, 0.69 mmol) in DMF (5 mL) was added CuI (4.4 mg, 0.023 mmol), $Pd(PPh_3)_2Cl_2$ (16 mg, 0.023 mmol), and TEA (69.6 mg, 0.69 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 4 hours. After cooling, the mixture was concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L HCOOH), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the yellow solid (1.33 mg, 1.47% yield).

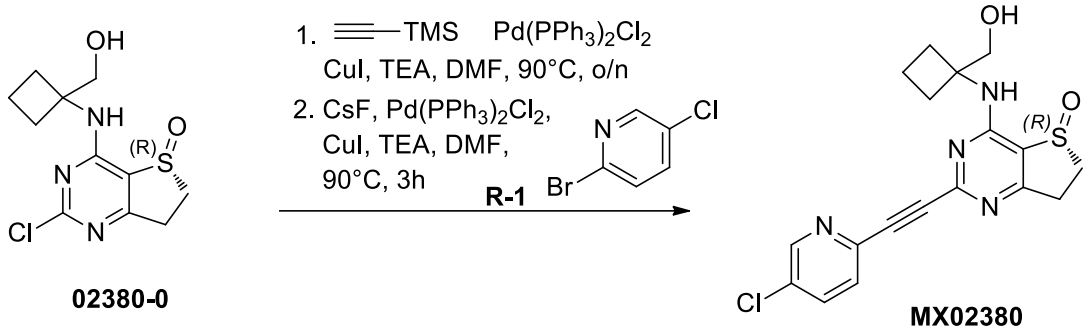
ESI-MS *m/z* calcd for $[C_{17}H_{16}ClFN_3O_2S_2]$ $[M+H]^+$:394.0; found:394.0

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.35 (d, *J* = 4.0 Hz, 1H), 7.30 (d, *J* = 4.0 Hz, 1H), 3.95 – 3.94 (m, 2H), 3.72 – 3.66 (m, 1H), 3.51 – 3.40 (m, 1H), 3.28 – 3.12 (m, 2H), 2.37 – 2.33 (m, 4H), 1.94 – 1.88 (m, 2H).



MX02380

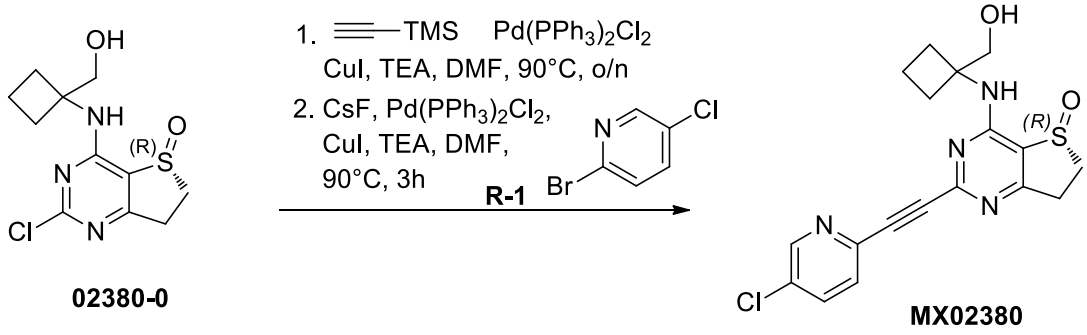
1. Synthetic scheme:



2. Experimental section:

2.1

(R)-2-((5-Chloropyridin-2-yl)ethynyl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02380)

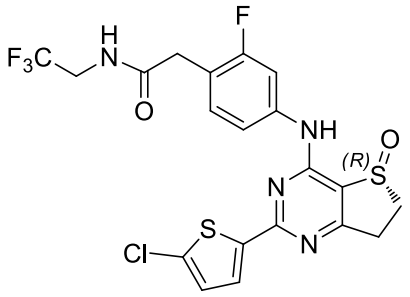


To a solution of (R)-2-chloro-4-[(1-(hydroxymethyl)cyclobutyl)amino]-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (50 mg, 0.174 mmol) and $Pd(PPh_3)_2Cl_2$ (12.3 mg, 0.018 mmol) in DMF (5 mL) was added TEA (53 mg, 0.522 mmol), trimethylsilylacetylene (34 mg, 0.348 mmol) and CuI (3.4 mg, 0.018 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C overnight. Then CsF (53 mg, 0.348 mmol), 2-bromo-5-chloropyridine (33.6 mg, 0.174 mmol), $Pd(PPh_3)_2Cl_2$ (12.3 mg, 0.018 mmol), CuI (3.4 mg, 0.018 mmol) and TEA (53 mg, 0.522 mmol) were added and the mixture was stirred under a nitrogen atmosphere at 90 °C for 3 hours. The reaction mixture was concentrated in vacuo, and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm

19*250 mm, 20 mL/min, UV 254] to afford the white solid (1.5 mg, 2.2% yield).

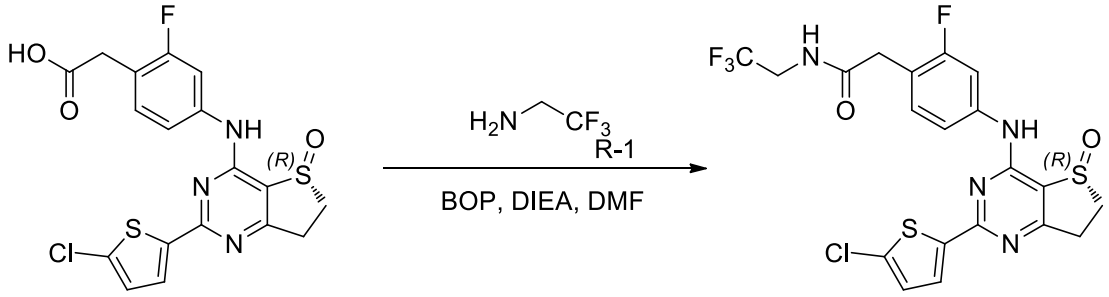
ESI-MS *m/z* calcd for [$C_{18}H_{17}ClN_4O_2S$] $[M+H]^+$: 389.1; found: 389.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 2.0 Hz, 1H), 8.28 (s, 1H), 8.05 (dd, J = 8.4, 2.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 4.91 (t, J = 5.6 Hz, 1H), 3.75 – 3.72 (m, 2H), 3.61 – 3.55 (m, 1H), 3.38 – 3.35 (m, 1H), 3.20 – 3.14 (m, 1H), 3.06 – 3.01 (m, 1H), 2.30 – 2.21 (m, 4H), 1.82 – 1.74 (m, 2H)



MX02387

1. Synthetic scheme:

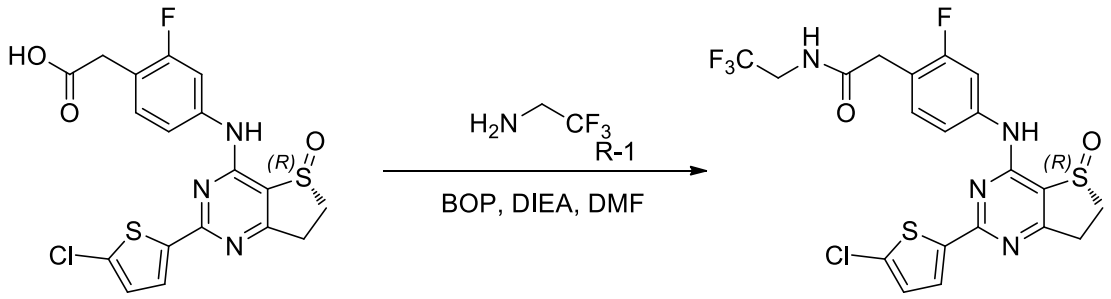


MX02159 **MX02387**

2. Experimental section:

2.1

(R)-2-(4-((2-(5-chloro-2-thienyl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-(2,2,2-trifluoroethyl) acetamide(MX02387)



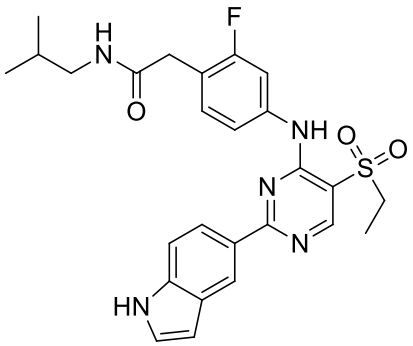
MX02159 **MX02387**

To a solution of (R)-2-(4-((2-(5-chlorothiophen-2-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (20 mg, 0.046 mmol) and 2,2,2-

trifluoroethylamine (13.6 mg, 0.14 mmol) in DMF (3 mL) was added BOP (40.4 mg, 0.091 mmol) and DIEA (23.6 mg, 0.18 mmol). The mixture was stirred at room temperature for 16 hours. The mixture was filtered and the filtrate was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (2.81 mg, 11.86% yield).

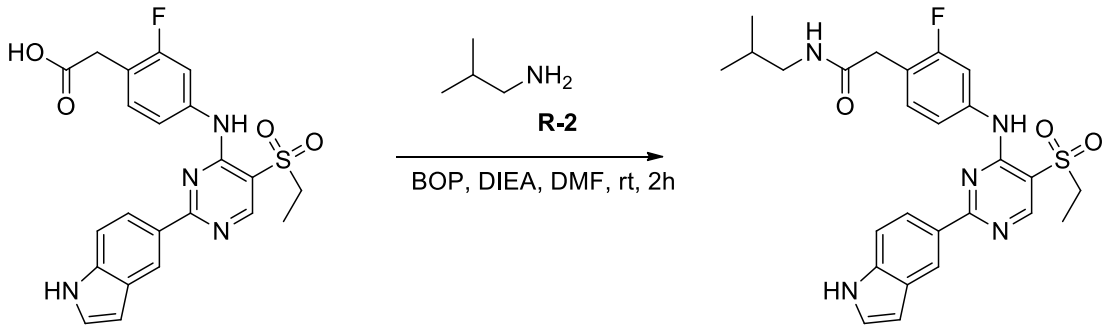
ESI-MS *m/z* calcd for [$C_{20}H_{15}ClF_4N_4O_2S_2$] $[M+H]^+$:519.0; found:518.8

^{1}H NMR (400 MHz,DMSO-d_6) δ10.25 – 10.22 (m, 1H), 8.78 (t, *J* = 6.0 Hz, 1H), 7.75 (d, *J* = 4.0 Hz, 1H), 7.67 (dd, *J* = 12.4, 2.0 Hz, 1H), 7.54 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 4.0 Hz, 1H), 3.99 – 3.90 (m, 2H), 3.77 – 3.69 (m,1H), 3.59 (s, 2H), 3.47 – 3.40 (m, 1H), 3.30 – 3.27 (m,1H), 3.16 – 3.11 (m, 1H).



MX02419

1. Synthetic scheme:

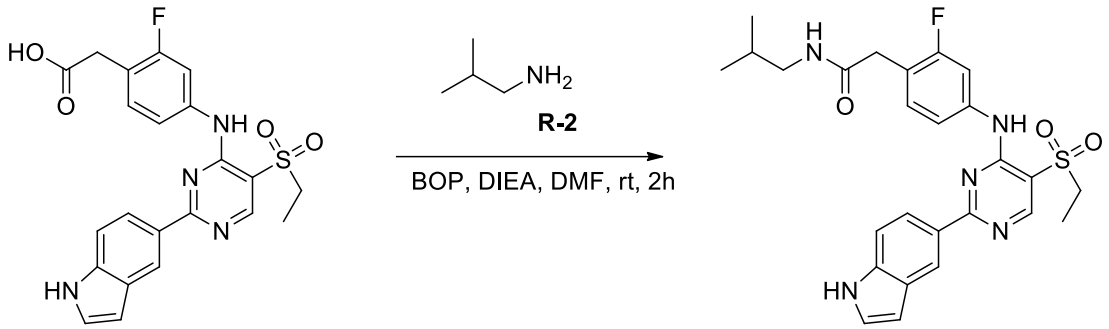


02419-0 **MX02419**

2. Experimental section:

2.1

2-(4-((5-(Ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutylethanamide(02159-1)

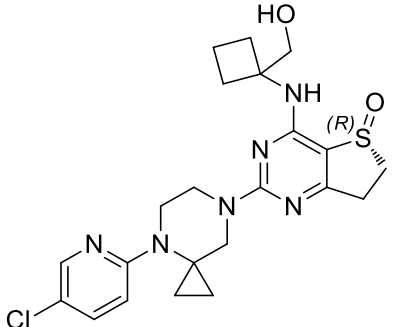


02419-0 MX02419

To a solution of 2-(4-((5-(ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (5 mg, 0.01 mmol) in DMF (3 mL) was added BOP (7.07 mg, 0.01 mmol), DIEA (4.26 mg, 0.03 mmol) and isobutylamine (1.16 mg, 0.01 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature for 2 hours until the starting material was consumed. The reaction mixture was concentrated in vacuo and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (2.18 mg, 38.9% yield).

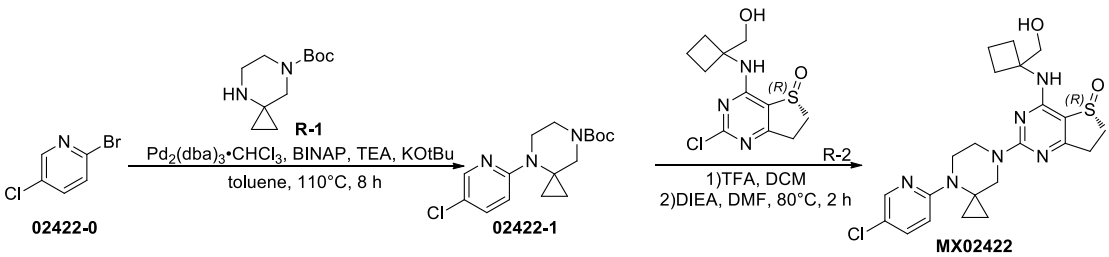
ESI-MS *m/z* calcd for $[C_{26}H_{28}FN_5O_3S]$ $[M+H]^+$: 510.2; found: 509.6

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 9.10 (s, 1H), 8.77 (s, 1H), 8.65 (s, 1H), 8.13 (dd, J = 8.4, 1.2 Hz, 1H), 8.08 (t, *J* = 5.2 Hz, 1H), 7.76 (dd, J = 12.0, 2.0 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.37 (m, 3H), 6.58 – 6.55 (m, 1H), 3.56 – 3.50 (m, 4H), 2.92 (t, *J* = 6.0 Hz, 2H), 1.75 – 1.68 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 6H).



MX02422

1. Synthetic scheme:

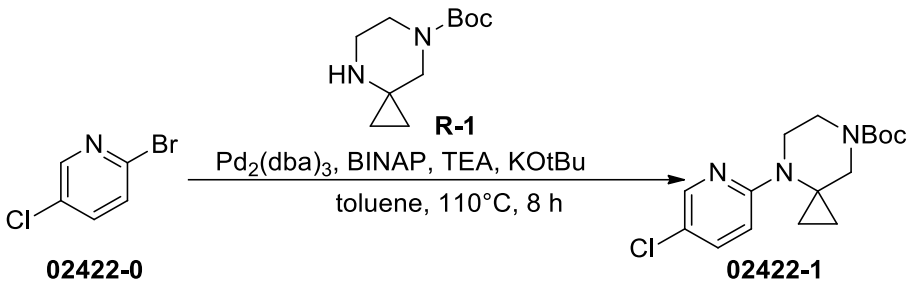


02422-0 02422-1 MX02422

2. Experimental section:

2.1

4-(5-Chloropyridin-2-yl)-4,7-diazaspiro[2.5]octane-7-carboxylic acid tert-butyl ester(02422-1)



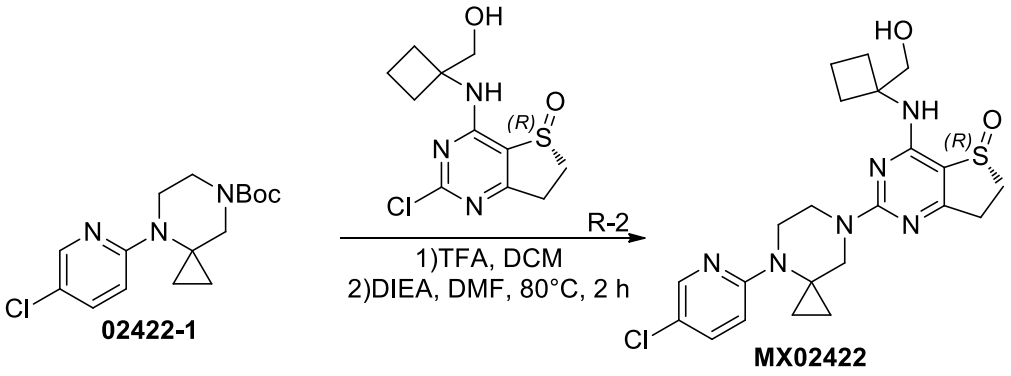
02422-0 02422-1

To a solution of 4,7-diazaspiro[2.5]octane-7-carboxylic acid tert-butyl ester (150 mg, 0.71 mmol) and 2-bromo-5-chloropyridine (149.6 mg, 0.78 mmol) in toluene (20 mL) was added $Pd_2(dba)_3$ (72.3 mg, 0.071 mmol), BINAP (66 mg, 0.11 mmol), t-BuOK (238 mg, 2.12 mmol) and TEA (215 mg, 2.12 mmol). The mixture was stirred under a nitrogen atmosphere at 110 °C for 8 hours. After cooling to room temperature, the reaction mixture was quenched with water and extracted with EA (20 mL) three times. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0 to 10%, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow syrup-like product (60 mg, 26.22% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{22}ClN_3O_2]$ $[M-56+H]^+$: 324.1; found: 324.2

2.2

(R)-2-(4-(5-Chloropyridin-2-yl)-4,7-diazaspiro[2.5] octan-7-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02422)



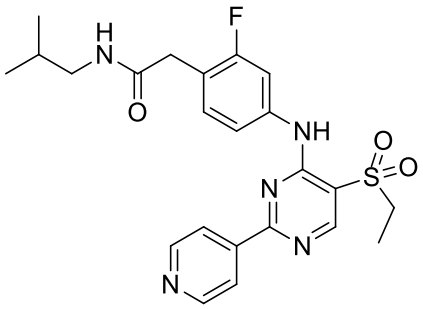
02422-1 MX02422

To a solution of 4-(5-chloropyridin-2-yl)-4,7-diazaspiro[2.5]octane-7-carboxylic acid tert-butyl ester (60 mg, 0.19 mmol) in DCM (4 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and the crude product was dissolved in DMF (3 mL). (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (40 mg, 0.14

mmol) and DIEA (89.8 mg, 0.70 mmol) were added to the solution. The mixture was stirred at 80 °C for 2 hours. The mixture was concentrated in vacuo, and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (26.16 mg, 39.62% yield).

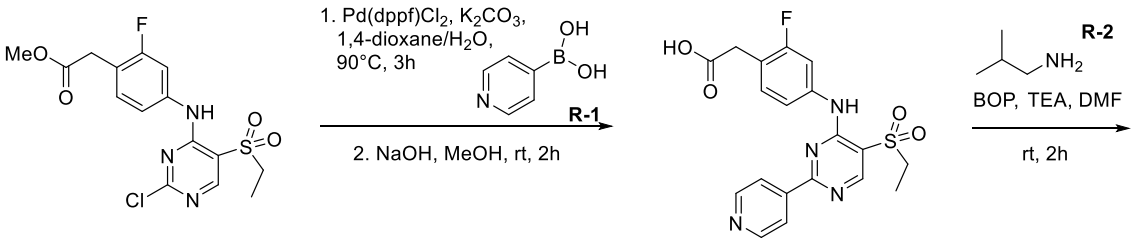
ESI-MS *m/z* calcd for [$C_{22}H_{27}ClN_6O_2S$] $[M+H]^+$: 475.2; found: 475.0

^{1}H NMR (400 MHz, Methanol-d_4) δ8.12 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 9.2, 2.8 Hz, 1H), 7.16 (d, J = 6.0 Hz, 1H), 4.01 – 3.81 (m, 8H), 3.58 – 3.50 (m, 1H), 3.39 – 3.34 (m, 1H), 3.08 – 3.01 (m, 2H), 2.35 – 2.26 (m, 4H), 1.93 – 1.86 (m, 2H), 1.01 – 0.92 (m, 4H).



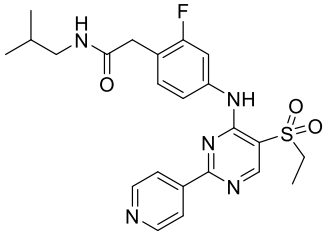
MX02423

1. Synthetic scheme:



02423-0

02423-1

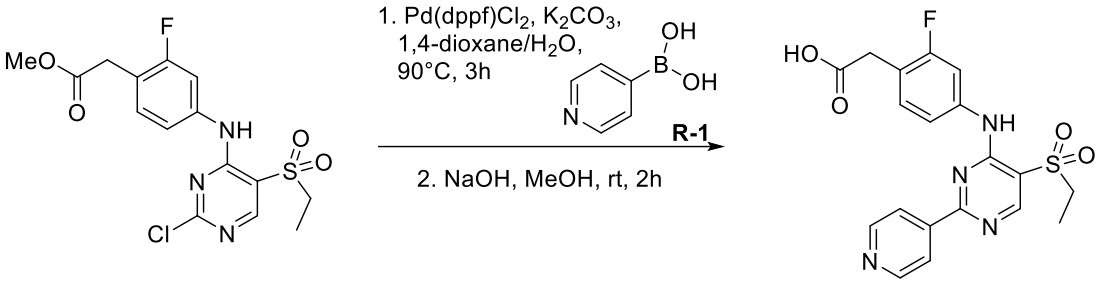


MX02423

2. Experimental section:

2.1

2-(4-(((5-(Ethylsulfonyl)-2-(pyridin-4-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (02423-1)



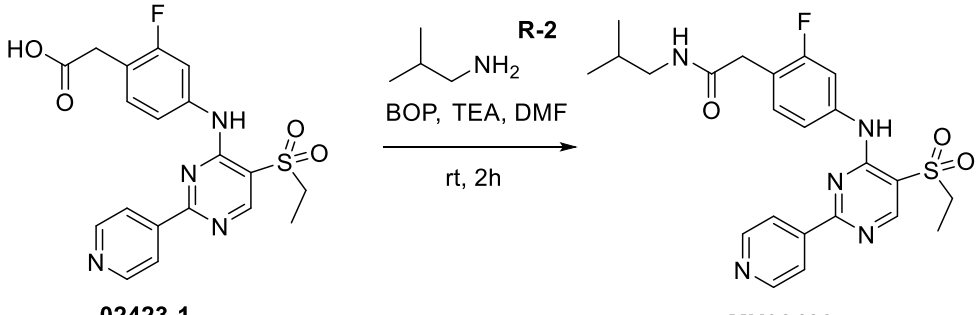
02423-0 02423-1

To a solution of methyl 2-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetate (40 mg, 0.104 mmol) and 4-pyridineboronic acid (15.3 mg, 0.124 mmol) in 1,4-dioxane/water (2 mL, v/v = 4/1) was added K_2CO_3 (43.1 mg, 0.312 mmol) and $Pd(dppf)Cl_2$ (7.3 mg, 0.01 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C for 3 hours. Then NaOH (41.6 mg, 1.04 mmol) and MeOH (1 mL) were added, and the mixture was further stirred at room temperature for 2 hours. The pH of the mixture was adjusted to 6 with 1N HCl aqueous solution and the solvent was removed in vacuo. The crude product was purified by reversed-phase column chromatography [$MeCN/H_2O$, 0/1 to 1/1, C-18 column, 40 mL/min, UV 254] to afford the pale yellow solid (15 mg, 34.7% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{17}FN_4O_4S]$ $[M+H]^+$: 417.1; found: 417.

2.2

2-(4-((5-(Ethylsulfonyl)-2-(pyridin-4-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutylethanamide (MX02423)

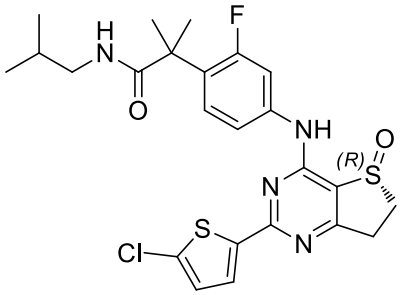


02423-1 MX02423

To a solution of 2-(4-(((5-(ethylsulfonyl)-2-(pyridin-4-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)acetic acid (15 mg, 0.036 mmol) in DMF (2 mL) was added isobutylamine (6 mg, 0.072 mmol), BOP (24 mg, 0.054 mmol) and TEA (12 mg, 0.108 mmol). The mixture was stirred at room temperature for 2 hours and the reaction mixture was concentrated to remove the solvent. The crude product was purified by preparative HPLC [$MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (9 mg, 53% yield).

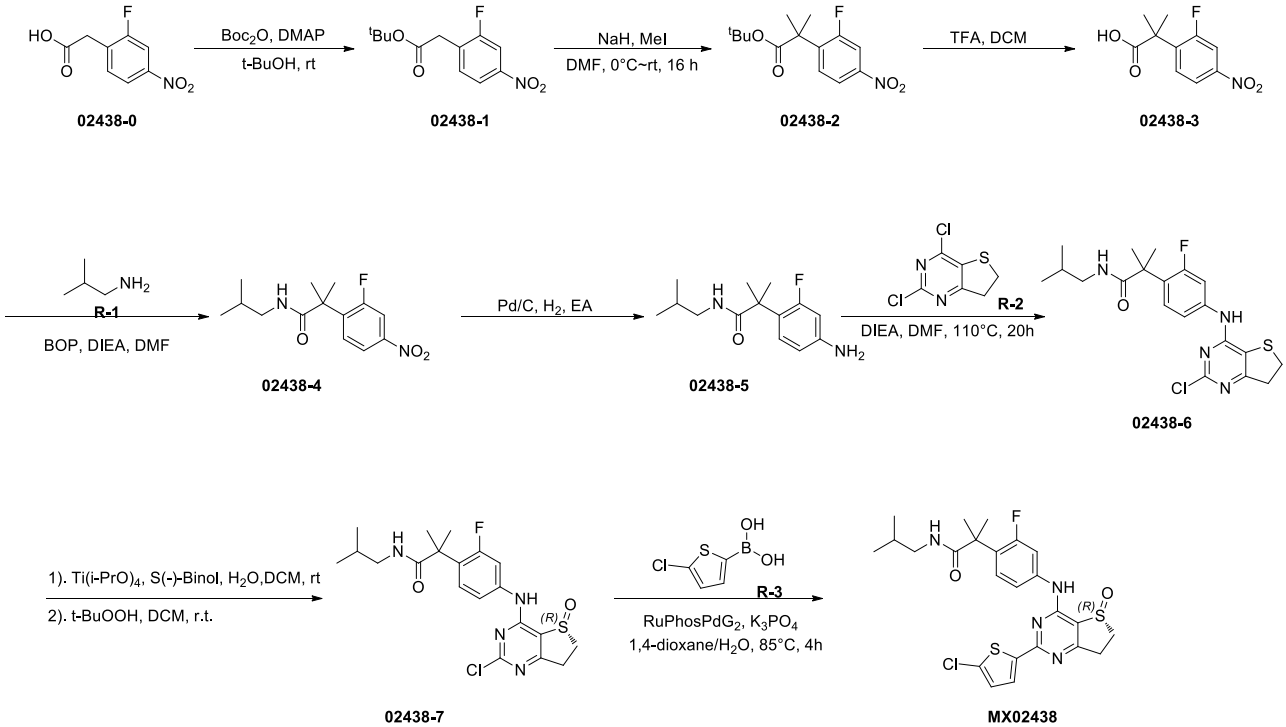
ESI-MS *m/z* calcd for $[C_{23}H_{26}FN_5O_3S]$ $[M+H]^+$: 472.2; found: 472.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.88 (s, 1H), 8.80 (d, J = 5.6 Hz, 2H), 8.13 (d, J = 5.2 Hz, 2H), 8.09 – 8.05 (m, 1H), 7.63 (d, J = 11.6 Hz, 1H), 7.43 – 7.39 (m, 2H), 3.60 – 3.54 (m, 2H), 3.51 (s, 2H), 2.91 (t, J = 6.0 Hz, 2H), 1.74 – 1.67 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.86 (s, 3H) , 0.83 (s, 3H).



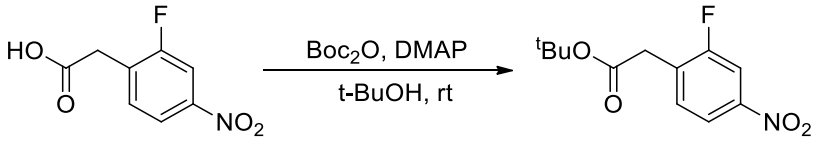
MX02438

1. Synthetic scheme:



2. Experimental section:

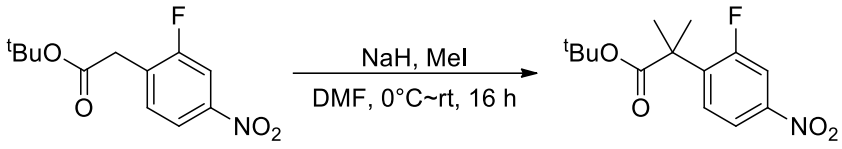
2.1 tert-Butyl 2-(2-fluoro-4-nitrophenyl)acetate(02438-1)



02438-0 **02438-1**

To a solution of 2-(2-fluoro-4-nitrophenyl)acetic acid (7.0 g, 35.15 mmol) in tert-butyl alcohol (150 mL) was added di-tert-butyl dicarbonate (8.44 g, 38.67 mmol) and DMAP (0.43 g, 3.52 mmol). The mixture was stirred at room temperature for 24 hours. Saturated aqueous $NaHCO_3$ solution (150 mL) was added and the mixture was stirred for 30 minutes. The mixture was extracted with EA (150 mL) twice. The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0 to 10%, silica gel, 40 g, 50 mL/min, UV 254) to afford the colorless oil (6.0 g, 66.87% yield).

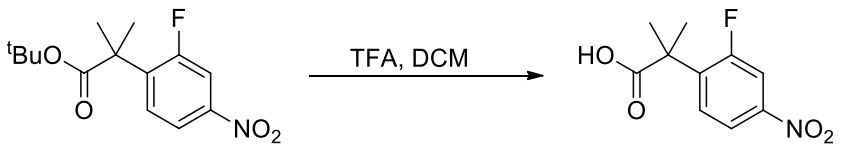
2.2 tert-Butyl 2-(2-fluoro-4-nitrophenyl)-2-methylpropanoate(02438-2)



02438-1 **02438-2**

To a solution of tert-butyl 2-(2-fluoro-4-nitrophenyl)acetate (60 g, 23.51 mmol) in DMF (50 mL) was added NaH (60%, 2.82 g, 70.52 mmol). The mixture was stirred at room temperature for 30 minutes, then cooled to 0 °C. Iodomethane (13.35 g, 94.03 mmol) was added, and the mixture was stirred at room temperature for 16 hours. Water (150 mL) was added and the mixture was extracted with EA (150 mL) twice. The combined organic layers were washed with saturated brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0 to 8%, silica gel, 80 g, 50 mL/min, UV 254) to afford the colorless oil (5.4 g, 81.09% yield).

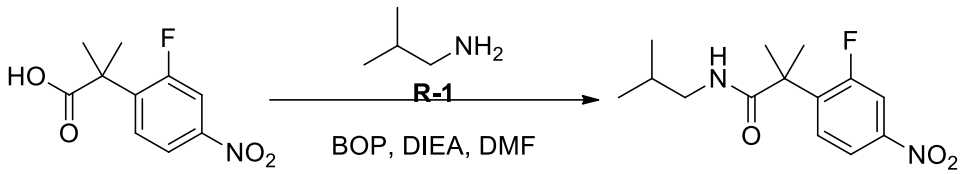
2.3 2-(2-Fluoro-4-nitrophenyl)-2-methylpropanoic acid(02438-3)



02438-2 **02438-3**

To a solution of tert-butyl 2-(2-fluoro-4-nitrophenyl)-2-methylpropanoate (1.4 g, 4.94 mmol) in DCM (25 mL) was added TFA (5 mL). The mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo to afford the white solid (1.1 g, 97.98% yield).

2.4 2-(2-Fluoro-4-nitrophenyl)-N-isobutyl-2-methylpropanamide(02438-4)

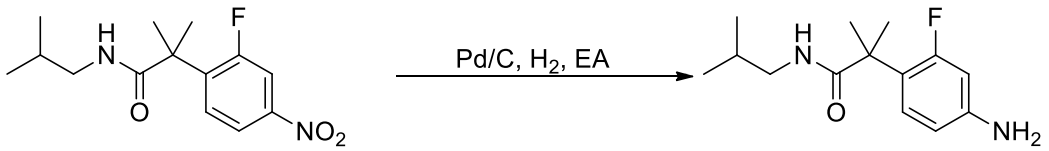


02438-3 **02438-4**

To a solution of 2-(2-fluoro-4-nitrophenyl)-2-methylpropanoic acid (1.1 g, 4.84 mmol) in DMF (20 mL) was added isobutylamine (1.06 g, 14.53 mmol), BOP (4.28 g, 9.68 mmol) and DIEA (1.88 g, 14.5 mmol). The mixture was stirred at room temperature for 16 hours and then poured into water (50 mL). The mixture was extracted with EA (50 mL) twice. The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE= 0 to 50%, silica gel, 40 g, 50 mL/min, UV 254) to afford the colorless oil (1.2 g, 87.79% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{19}FN_2O_3]$ $[M+H]^+$:283.1; found:283.2

2.5 2-(4-Amino-2-fluorophenyl)-N-isobutyl-2-methylpropanamide(02438-5)



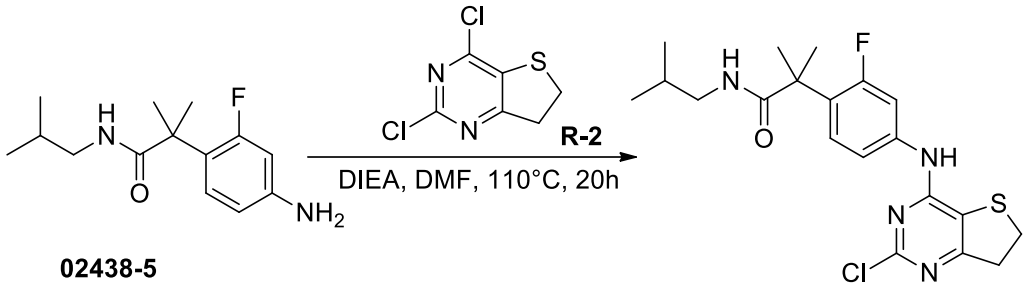
02438-4 **02438-5**

To a solution of 2-(2-fluoro-4-nitrophenyl)-N-isobutyl-2-methylpropanamide (1.2 g, 4.25 mmol) in EA (40 mL) was added Pd/C (0.2 g). The mixture was stirred under a hydrogen atmosphere at room temperature for 16 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (EA/PE= 0 to 70%, silica gel, 40 g, 50 mL/min, UV 254) to afford the colorless oil (1.05 g, 97.90% yield).

ESI-MS m/z calcd for $[C_{14}H_{21}FN_2O]$ $[M+H]^+$:253.2; found:253.3

2.6

2-(4-((2-Chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutyl-2-methylpropanamide(02438-6)



02438-5

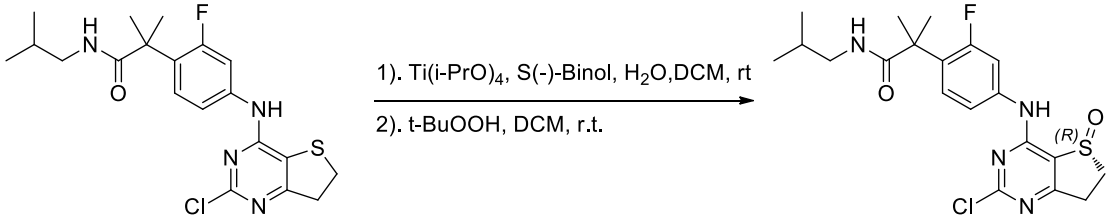
02438-6

To a solution of 2-(4-amino-2-fluorophenyl)-N-isobutyl-2-methylpropanamide (250 mg, 0.99 mmol) and 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidine (616 mg, 2.97 mmol) in DMF (10 mL) was added DIEA (512 mg, 3.96 mmol). The mixture was stirred at 110 °C for 20 hours. After the reaction was complete, the mixture was concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0 to 75%, silica gel, 20 g, 25 mL/min, UV 254) to afford the yellow solid (192 mg, 45.82% yield).

ESI-MS *m/z* calcd for $[C_{20}H_{24}ClFN_4OS]$ $[M+H]^+$:423.1; found:423.1

2.7

(R)-2-(4-((2-chloro-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutyl-2-methylpropanamide(02438-7)



02438-6

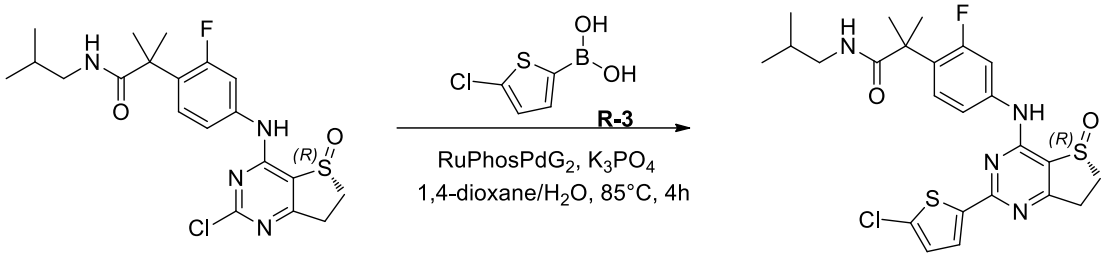
02438-7

To a solution of 2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutyl-2-methylpropanamide (192 mg, 0.454 mmol) in DCM (10 mL) was added S-1,1'-biphenyl-2,2'-diol (26 mg, 0.09 mmol), titanium isopropoxide (26 mg, 0.09 mmol) and water (16 mg, 0.91 mmol). The mixture was stirred at room temperature for 16 hours. Then 70% tert-butyl hydroperoxide aqueous solution (175 mg, 1.36 mmol) was added and the mixture was stirred at room temperature for 2 hours. Water (10 mL) was added and the mixture was extracted with DCM (30 mL) three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (MeOH/DCM= 0 to 5%, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (103 mg, 51.69% yield).

ESI-MS *m/z* calcd for $[C_{20}H_{24}ClFN_4O_2S]$ $[M+H]^+$:439.1; found:439.0

2.8

(R)-1-(4-((2-(5-Chlorothien-2-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutylcyclopropanecarboxamide(MX02438)

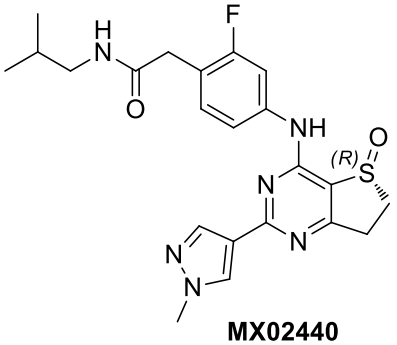


02438-7 MX02438

To a solution of (R)-2-(4-((2-chloro-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutyl-2-methylpropanamide (40 mg, 0.09 mmol) in 1,4-dioxane/water (5 mL, v/v = 4:1) was added 5-chlorothiophen-2-ylboronic acid (29 mg, 0.18 mmol), K_3PO_4 (58 mg, 0.27 mmol) and RuPhosPdG2 (14 mg, 0.02 mmol). The mixture was stirred under a nitrogen atmosphere at 85 °C for 4 hours. After the reaction was complete, the mixture was concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the light yellow solid (11.47 mg, 24.16% yield).

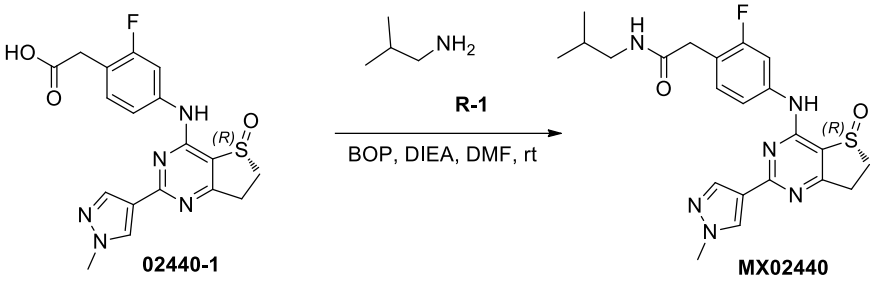
ESI-MS *m/z* calcd for $[C_{24}H_{26}ClFN_4O_2S_2]$ $[M+H]^+$:521.1; found: 520.8

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.77 (d, *J* = 4.0 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.43 (t, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 4.0 Hz, 1H), 7.22 (t, *J* = 6.0 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.48 – 3.40 (m, 1H), 3.34 – 3.23 (m, 1H), 3.16 – 3.11 (m, 1H), 2.88 – 2.82 (m, 2H), 1.76 – 1.69 (m, 1H), 1.46 (s, 6H), 0.79 (d, *J* = 6.8 H, 6H).



MX02440

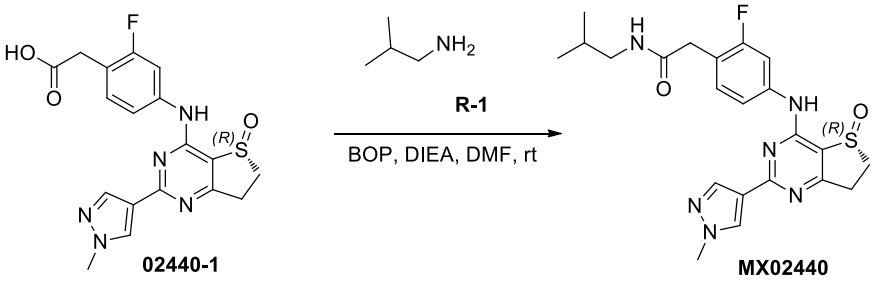
1. Synthetic scheme:



2. Experimental section:

2.1

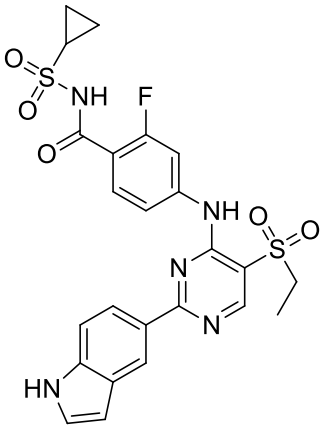
(R)-2-(2-Fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)-N-isobutylacetamide (MX02440)



To a solution of (R)-2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl)acetic acid (20 mg, 0.05 mmol) in DMF (2 mL) was added isobutylamine (4 mg, 0.06 mmol), DIEA (19 mg, 0.15 mmol) and BOP (33 mg, 0.075 mmol). The mixture was stirred at room temperature for 1 hour until the starting material was consumed. The reaction mixture was concentrated in vacuo and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (7.12 mg, 31% yield).

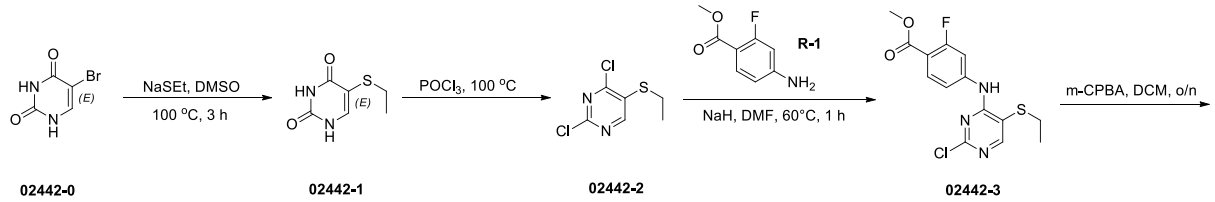
ESI-MS *m/z* calcd for [$C_{22}H_{25}FN_6O_2S$] $[M+H]^+$: 457.2; found: 456.6

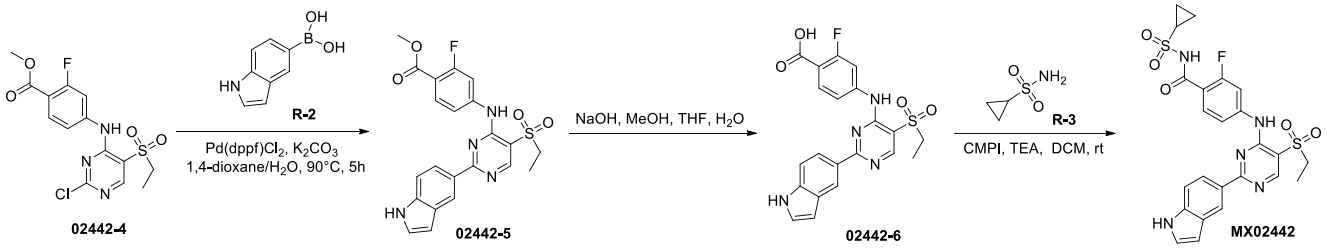
^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.31 (s, 1H), 8.04 (t, *J* = 5.6 Hz, 1H), 7.95 (s, 1H), 7.69 – 7.61 (m, 2H), 7.33 (t, *J* = 8.8 Hz, 1H), 3.91 (s, 3H), 3.73 – 3.65 (m, 1H) , 3.48 (s, 2H), 3.44 – 3.37 (m, 1H), 3.30 – 3.24 (m, 1H), 3.13 – 3.07 (m, 1H)， 2.91 (t, *J* = 6.0 Hz, 2H), 1.75 – 1.65 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 6H).



MX02442

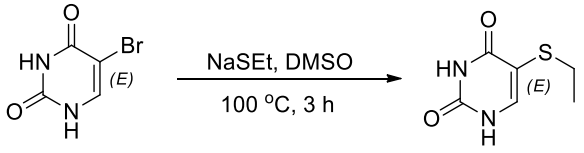
1. Synthetic scheme:





2. Experimental section:

2.1 5-(Ethylthio)pyrimidine-2,4(1H,3H)-dione(02442-1)



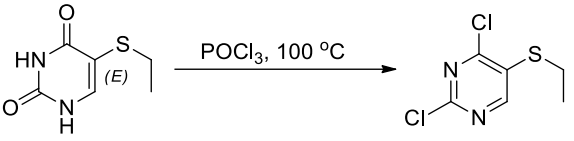
02442-0 **02442-1**

To a solution of 5-bromopyrimidine-2,4(1H,3H)-dione (1.5 g, 7.85 mmol) in DMSO (10 mL) was added NaSEt (659 mg, 7.85 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 3 hours until the starting material was consumed. Water (20 mL) was added to the reaction mixture and the mixture was extracted with EA (50 mL) five times. The

combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the white solid (730 mg, 56% yield).

ESI-MS *m/z* calcd for $[C_6H_8N_2O_2S]$ $[M+H]^+$: 173.0; found: 173.2

2.2 2,4-Dichloro-5-ethylthiopyrimidine(02442-2)



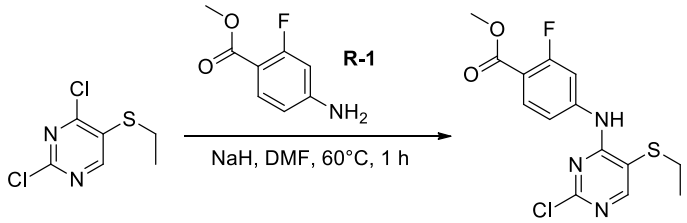
02442-1 02442-2

To a solution of 5-(ethylthio)pyrimidine-2,4(1H,3H)-dione (700 mg, 4.07 mmol) in $POCl_3$ (5 mL) was stirred under a nitrogen atmosphere at 100 °C overnight until the starting material was consumed. Water (20 mL) was added to the mixture and the mixture was extracted with EA (40 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0/1 to 1/10, silica gel, 40 g, 40 mL/min, UV 254) to afford the yellow solid (152 mg, 18% yield).

ESI-MS *m/z* calcd for $[C_6H_6Cl_2N_2S]$ $[M+H]^+$: 209.0; found: 209.0

2.3

Methyl 4-((2-chloro-5-(ethylthio)pyrimidin-4-yl)amino)-2-fluorobenzoate (02442-3)



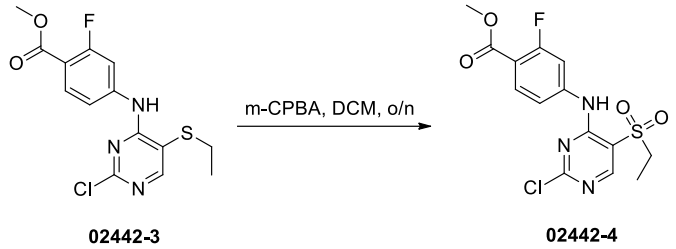
02442-2 02442-3

To a solution of 2,4-dichloro-5-(ethylthio)pyrimidine (300 mg, 1.46 mmol) in DMF (3 mL) was added methyl 4-amino-2-fluorobenzoate (247 mg, 1.46 mmol) and NaH (117 mg, 2.92 mmol). The mixture was stirred under a nitrogen atmosphere at 60 °C for 1 hour until the starting material was consumed (monitored by LCMS). Water (20 mL) was added to quench the reaction mixture and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (EA/PE, 0/1 to 1/1, silica gel, 40 g, 20 mL/min, UV 254) to afford the yellow solid (317 mg, 65% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{13}ClFN_3O_2S]$ $[M+H]^+$: 342.0; found: 342.0

2.4

Methyl4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorobenzoate(02442-4)



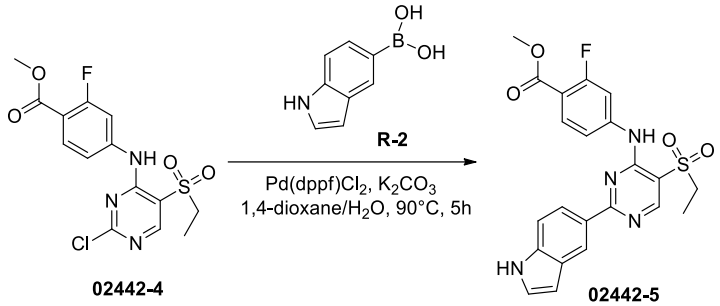
02442-3 02442-4

To a solution of methyl 4-((2-chloro-5-(ethylthio)pyrimidin-4-yl)amino)-2-fluorobenzoate (300 mg, 0.88 mmol) in DCM (5 mL) was added m-CPBA (85%, 534 mg, 2.64 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature overnight until the starting material was consumed (monitored by LCMS). The reaction mixture was quenched with 10 mL of saturated $NaHCO_3$ solution and extracted with EA (30 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (EA/PE=0/1 to 1/4, silica gel, 20 g, 20 mL/min, UV 254) to afford the white solid (280 mg, 85% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{13}ClFN_3O_4S]$ $[M+H]^+$: 374.0; found: 374.2

2.5

Methyl4-((5-(ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorobenzoate(02442-5)



02442-4 02442-5

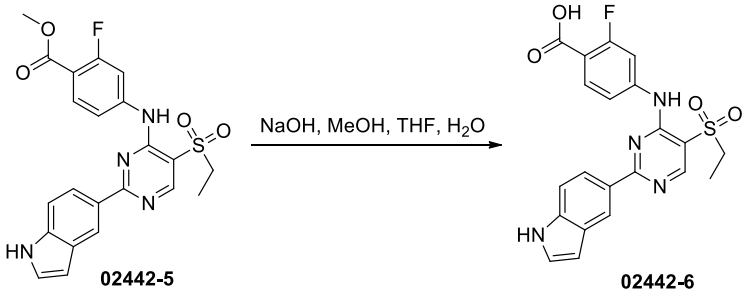
To a solution of methyl 4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorobenzoate (250 mg, 0.67 mmol) in 1,4-dioxane/water (2.5 mL, v/v = 5/1) was added 1H-indol-5-ylboronic acid (129 mg, 0.80 mmol), K_2CO_3 (185 mg, 1.34 mmol) and $Pd(dppf)Cl_2$ (48 mg, 0.067 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C for 5 hours. Water (10 mL) was added and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column

chromatography (EA/PE, 0/1 to 1/1, silica gel, 40 g, 40 mL/min, UV 254) to afford the yellow solid (215 mg, 71% yield).

ESI-MS *m/z* calcd for $[C_{22}H_{19}FN_4O_4S]$ $[M+H]^+$: 455.1; found: 455.2

2.6

4-((5-(Ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorobenzoic acid(02442-6)

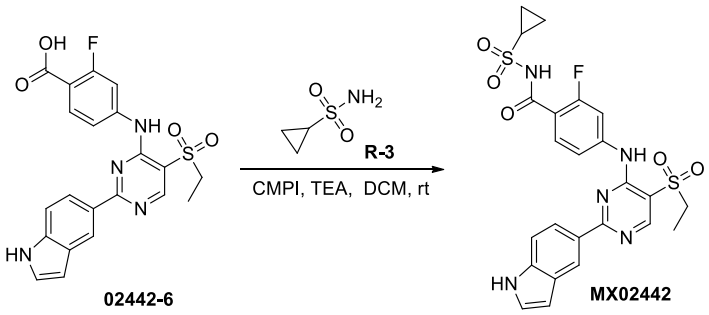


To a solution of methyl 4-((5-(ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorobenzoate (200 mg, 0.44 mmol) in MeOH/THF (4 mL, v/v = 1/1) was added 2N NaOH aqueous solution to adjust the pH to 12. The mixture was stirred under a nitrogen atmosphere at room temperature for 3 hours until the starting material was consumed. The pH of the mixture was adjusted to 6 with 1N HCl aqueous solution. The mixture was concentrated, and the crude product was purified by reversed-phase column chromatography [MeCN/H_2O, 0 to 3/17, C-18 column, 50 mL/min, UV 214] to afford the white solid (147 mg, 76% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{17}FN_4O_4S]$ $[M+H]^+$: 441.1; found: 441.1

2.7

N-(Cyclopropylsulphonyl)-4-((5-(ethylsulphonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorobenzamide(MX02442)

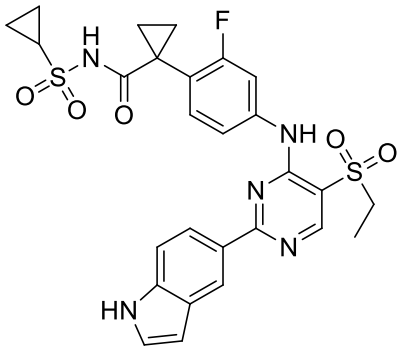


To a solution of 4-((5-(ethylsulfonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorobenzoic acid (50 mg, 0.11 mmol) and cyclopropanesulfonamide (14 mg, 0.11 mmol) in DCM (4 mL) was added TEA (22 mg, 0.22 mmol) and CMPI (56 mg, 0.22 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature for 1 hour. Water (10 mL) was added and the mixture was extracted with EA (20 mL) three times. The combined organic

layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (5.03 mg, 8% yield).

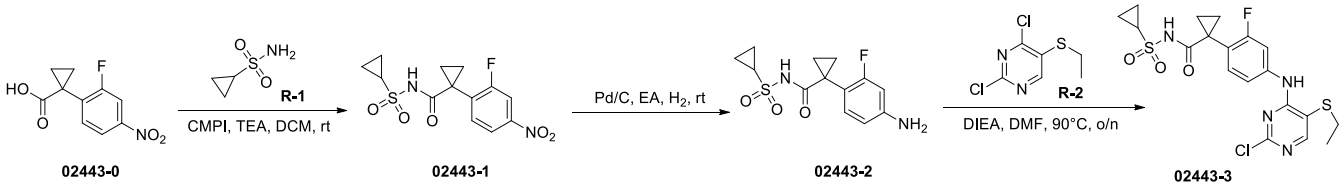
ESI-MS *m/z* calcd for $[C_{24}H_{22}FN_5O_5S_2]$ $[M+H]^+$: 544.1; found: 544.2

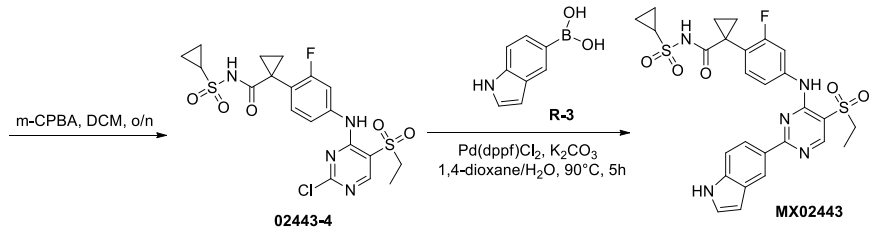
^{1}H NMR (400 MHz, DMSO-d_6) δ12.10 (s, 1H), 11.46 (s, 1H), 9.32 (s, 1H), 8.84 (s, 1H), 8.68 (s, 1H), 8.16 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.95 (d, *J* = 13.2 Hz, 1H), 7.80 (t, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H) , 7.46 (t, *J* = 2.8 Hz, 1H), 6.61 (s, 1H), 3.56 (q, *J* = 7.2 Hz, 2H), 3.14 – 3.07 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.16 – 1.08 (m, 4H).



MX02443

1. Synthetic scheme:

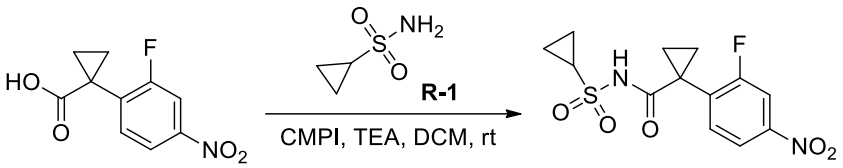




2. Experimental section:

2.1

N-(Cyclopropylsulphonyl)-1-(2-fluoro-4-nitrophenyl)cyclopropanecarboxamide(02443-1)



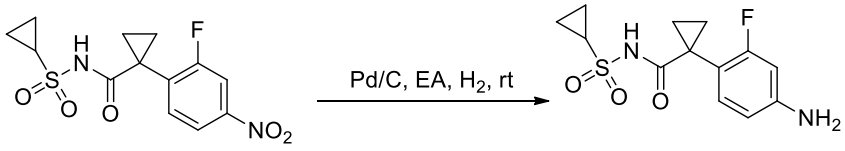
02443-0 02443-1

To a solution of 1-(2-fluoro-4-nitrophenyl)cyclopropanecarboxylic acid (430 mg, 1.91 mmol) and cyclopropanesulfonamide (231 mg, 1.91 mmol) in DCM (10 mL) was added TEA (386 mg, 3.82 mmol) and CMPI (974 mg, 3.82 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature for 1 hour. Water (10 mL) was added and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0 to 70%, silica gel, 40 g, 40 mL/min, UV 254) to afford the colorless oil (411 mg, 65% yield).

ESI-MS m/z calcd for $[C_{13}H_{13}FN_2O_5S]$ $[M+H]^+$:329.1; found: 329.2.

2.2

1-(4-Amino-2-fluorophenyl)-N-(cyclopropylsulfonyl)cyclopropanecarboxamide(02443-2)



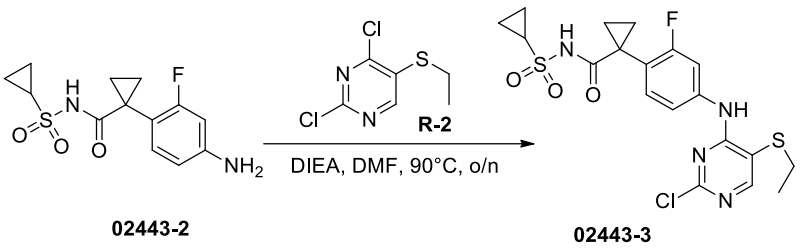
02443-1 02443-2

To a solution of N-(cyclopropanesulfonyl)-1-(2-fluoro-4-nitrophenyl)cyclopropanecarboxamide (411 mg, 1.25 mmol) in EA (10 mL) was added Pd/C (40 mg). The mixture was stirred under a hydrogen atmosphere at room temperature for 16 hours. After the reaction was complete, the mixture was filtered under reduced pressure and the filtrate was concentrated in vacuo to afford the white solid (368 mg, 98% yield).

ESI-MS m/z calcd for $[C_{13}H_{15}FN_2O_3S]$ $[M+H]^+$:299.1; found:299.2

2.3

1-(4-((2-Chloro-5-(ethylthio)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-(cyclopropanesulfonyl)cyclopropanecarboxamide(02443-3)



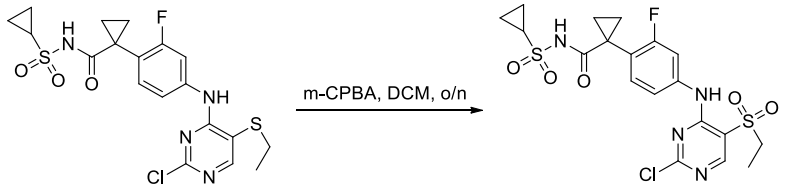
02443-2 02443-3

To a solution of N-(cyclopropanesulfonyl)-1-(4-amino-2-fluorophenyl)cyclopropanecarboxamide (100 mg, 0.33 mmol) and 2,4-dichloro-5-(ethylthio)pyrimidine (68 mg, 0.33 mmol) in DMF (3 mL) was added DIEA (128 mg, 1.00 mmol). The mixture was stirred at 90 °C overnight. After the starting materials were consumed (monitored by LCMS), water (10 mL) was added and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0/1 to 1, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (103 mg, 65% yield).

ESI-MS m/z calcd for $[C_{19}H_{20}ClFN_4O_3S_2]$ $[M+H]^+$:471.1; found:471.1

2.4

1-(4-((2-Chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-(cyclopropylsulfonyl)cyclopropanecarboxamide(02443-4)



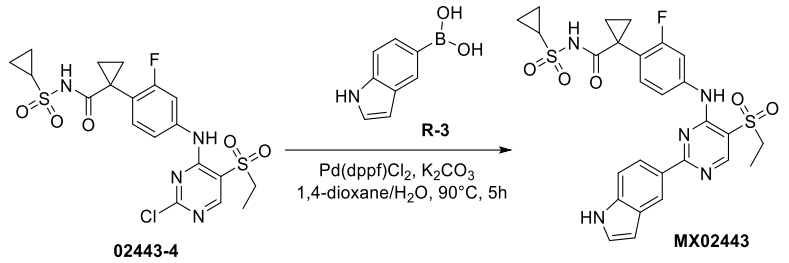
02443-3 02443-4

To a solution of 1-(4-((2-chloro-5-(ethylthio)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-(cyclopropanesulfonyl)cyclopropanecarboxamide (100 mg, 0.21 mmol) in DCM (5 mL) was added m-CPBA (85%, 127 mg, 0.63 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature overnight. After the starting material was consumed (monitored by LCMS), saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0/1 to 1/4, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (92 mg, 86% yield).

ESI-MS m/z calcd for $[C_{19}H_{20}ClFN_4O_5S_2]$ $[M+H]^+$:503.1; found:503.2

2.5

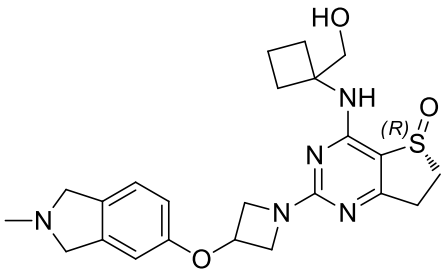
N-(Cyclopropylsulphonyl)-1-(4-((5-(ethylsulphonyl)-2-(1H-indol-5-yl)pyrimidin-4-yl)amino)-2-fluorophenyl)cyclopropanecarboxamide(MX02443)



To a solution of 1-(4-((2-chloro-5-(ethylsulfonyl)pyrimidin-4-yl)amino)-2-fluorophenyl)-N-(cyclopropanesulfonyl)cyclopropanecarboxamide (30 mg, 0.06 mmol) in 1,4-dioxane/water (2.5 mL, v/v = 4/1) was added 1H-indol-5-ylboronic acid (12 mg, 0.07 mmol), K_2CO_3 (19 mg, 0.14 mmol) and $Pd(dppf)Cl_2$ (4 mg, 0.006 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C for 5 hours. After the starting materials were consumed (monitored by LCMS), the reaction mixture was concentrated. The crude product was purified by preparative HPLC [$MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (3.67 mg, 11% yield).

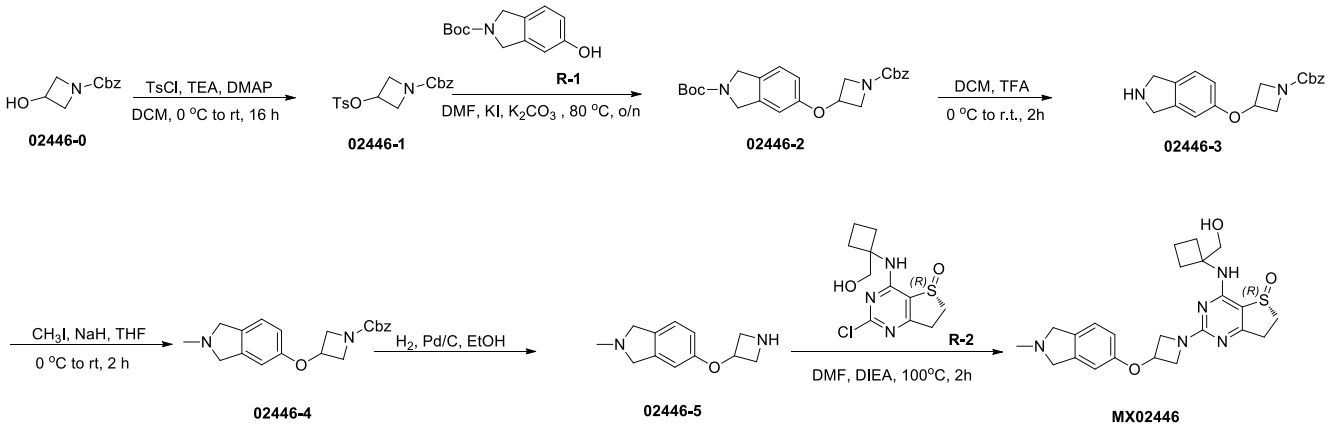
ESI-MS *m/z* calcd for $[C_{27}H_{26}FN_5O_5S_2]$ $[M+H]^+$:584.1; found: 584.2

^1H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 11.09 (s, 1H), 9.17 (s, 1H), 8.80 (s, 1H), 8.68 (s, 1H), 8.17 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.82 (d, *J* = 11.6 Hz, 1H), 7.53 – 7.41 (m, 4H), 6.60 (t, *J* = 2.0 Hz, 1H), 3.53 (q, *J* = 7.2 Hz, 2H), 2.97 –2.95 (m, 1H), 1.66 – 1.56 (m, 2H), 1.28 – 1.24 (m, 5H), 1.12 – 1.02 (m, 4H).



MX02446

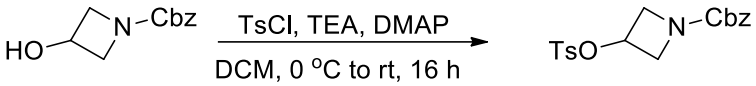
1. Synthetic scheme:



2. Experimental section:

2.1

3-(p-Toluenesulfonyl)azetidine-1-carboxylic acid benzyl ester(02446-1)



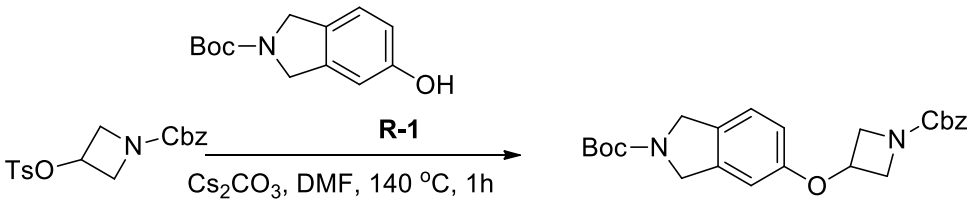
02446-0 **02446-1**

To a solution of 1-(benzyloxycarbonyl)-3-hydroxyazetidine (2 g, 9.65 mmol) in DCM (30 mL) at 0 °C was added p-toluenesulfonyl chloride (3.67 g, 19.3 mmol), TEA (2.92 g, 28.95 mmol) and DMAP (117.3 mg, 0.96 mmol). The mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated in vacuo and the crude product was purified by column chromatography (EA/PE=0 to 25%, silica gel, 40 g, 50 mL/min, UV 254) to afford the yellow solid (2.6 g, 75.57% yield).

ESI-MS m/z calcd for $[C_{18}H_{19}NO_5S]$ $[M+H]^+$:362.1; found:362.0.

2.2

5-((1-((Benzyloxy)carbonyl)azetidin-3-yl)oxy)isoindoline-2-carboxylic acid tert-butyl ester(02446-2)



02446-1 **02446-2**

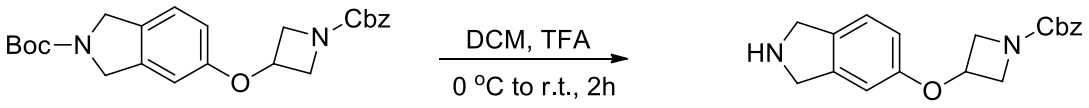
To a solution of 3-(p-toluenesulfonyloxy)azetidine-1-carboxylic acid benzyl ester (500 mg, 1.38 mmol) and 5-hydroxy-1H-isindoline-2-carboxylic acid tert-butyl ester (651 mg, 1.38 mmol) in DMF (15 mL) was added Cs_2CO_3 (1.35 g, 4.14 mmol). The mixture was stirred at 140 °C for 1 hour. Water (50 mL) was added and the mixture was extracted with EA (25 mL) twice. The combined organic layers were washed with saturated brine (50 mL), dried over

anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0 to 75%, silica gel, 20 g, 25 mL/min, UV 254) to afford the white solid (370 mg, 63.24% yield).

ESI-MS m/z calcd for $[C_{24}H_{28}N_2O_5]$ $[M-100+H]^+$:325.2; found:325.3.

2.3

Benzyl ester of 3-(isoindolin-5-yloxy)azetidine-1-carboxylic acid(02446-3)



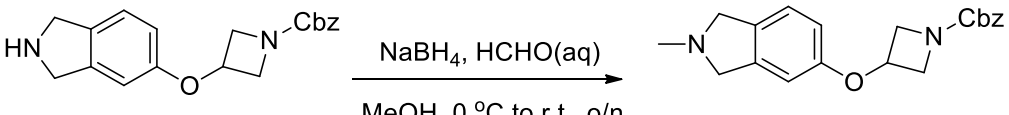
02446-2 **02446-3**

To a solution of 5-((1-((benzyloxycarbonyl)azetidin-3-yl)oxy)isindoline-2-carboxylic acid tert-butyl ester (170 mg, 0.400 mmol) in DCM (5 mL) at 0 °C was added TFA (0.5 mL). The mixture was stirred at room temperature for 2 hours after warming to room temperature. The pH of the mixture was adjusted to 8 with saturated aqueous $NaHCO_3$ solution and the mixture was extracted with EA (20 mL) twice. The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the colorless oil (200 mg, 71.0% yield).

ESI-MS m/z calcd for $[C_{19}H_{20}N_2O_3]$ $[M+H]^+$:325.2; found:325.3.

2.4

3-((2-Methylisoindolin-5-yl)oxy)azetidine-1-carboxylic acid benzyl ester (02446-4)

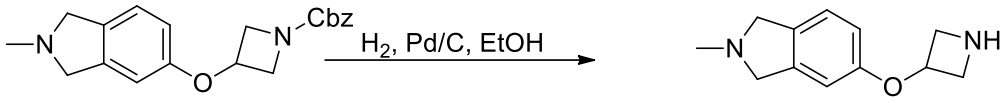


02446-3 **02446-4**

To a solution of 3-(isindoline-5-yl)azetidine-1-carboxylic acid benzyl ester (150 mg, 0.46 mmol) in MeOH (5 mL) at 0 °C was added formaldehyde aqueous solution (37%, 37 mg, 0.46 mmol) and $NaBH_4$ (26 mg, 0.69 mmol). The mixture was slowly warmed to room temperature and stirred for 2 hours until the starting material was consumed. The reaction mixture was quenched with saturated NH_4Cl aqueous solution (20 mL) at 0 °C and extracted with EA (15 mL) three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0~50%, silica gel, 12 g, 15 mL/min, UV 254) to afford the colorless oil (132 mg, 85.16% yield).

ESI-MS m/z calcd for $[C_{20}H_{22}N_2O_3]$ $[M+H]^+$:339.2; found:339.3.

2.5 5-(Aziridin-3-yloxy)-2-methylisoindoline(02446-5)



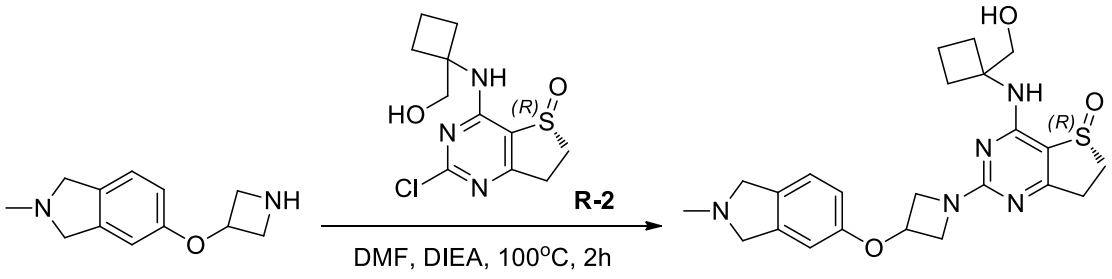
02446-4 02446-5

To a solution of 3-((2-methylisindolin-5-yl)oxy)azetidine-1-carboxylic acid benzyl ester (132 mg, 0.39 mmol) in EtOH (20 mL) was added Pd/C (13.2 mg). The mixture was stirred under a hydrogen atmosphere at room temperature for 16 hours, filtered through Celite and concentrated in vacuo. The crude product was purified by column chromatography (MeOH/DCM = 0~10%, silica gel, 12 g, 20 mL/min, UV 254) to afford the colorless oil (54 mg, 68.34% yield).

ESI-MS m/z calcd for $[C_{12}H_{16}N_2O]$ $[M+H]^+$:205.1; found:205.3

2.6

(R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(3-((2-methylisoindol-5-yl)oxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02446)

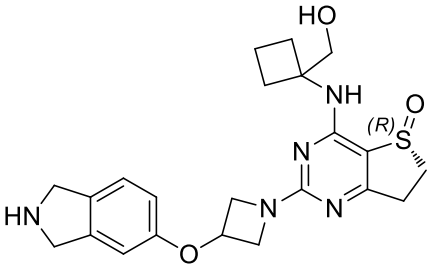


02446-5 MX02446

To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (75.92 mg, 0.26 mmol) in DMF (3 mL) was added 5-((azetidin-3-yl)oxy)-2-methylisindoline (54 mg, 0.26 mmol) and DIEA (100.8 mg, 0.78 mmol). The mixture was stirred at 100 °C for 2 hours and the reaction mixture was concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (3.64 mg, 3% yield).

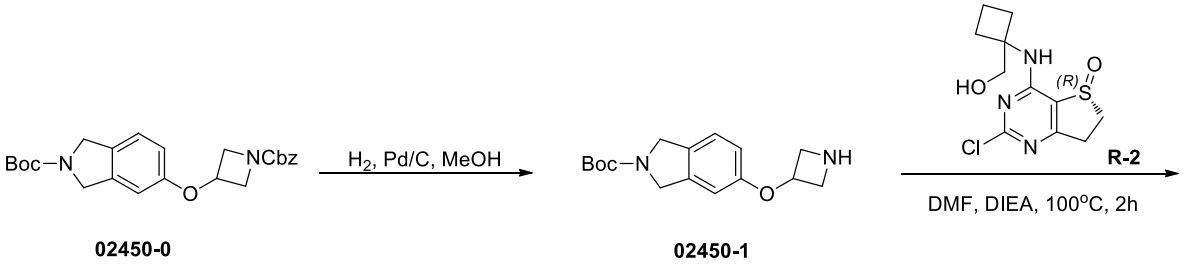
ESI-MS *m/z* calcd for $[C_{23}H_{29}N_5O_3S]$ $[M+H]^+$: 456.2; found: 456.4

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (s, 1H), 7.13(d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.10 – 5.05 (m, 1H), 4.84 (t, *J* = 6.0 Hz, 1H), 4.46 – 4.42 (m, 2H), 3.93 – 3.86 (m, 2H), 3.77 (s, 2H), 3.73 (s, 2H), 3.69 (d, *J* = 4.4 Hz, 2H), 3.45 – 3.34 (m, 1H), 3.25 –3.17 (m, 1H), 2.96 –2.84 (m, 2H), 2.46 (s, 3H), 2.38 –2.25 (m, 2H), 2.15 –2.08 (m, 2H), 1.79 –1.68 (m, 2H).

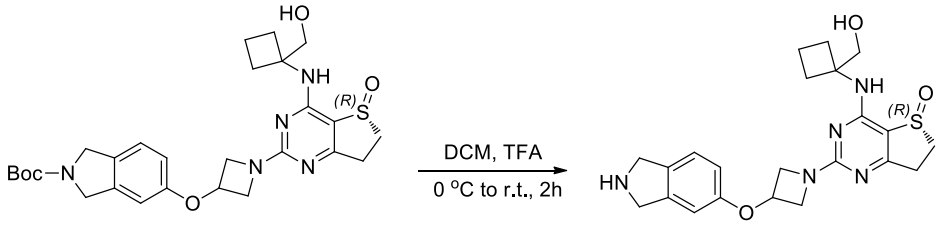


MX02450

1. Synthetic scheme:



02450-0 **02450-1**

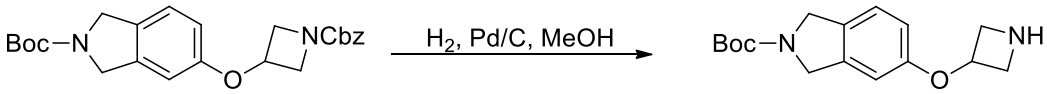


02450-2 **MX02450**

2. Experimental section:

2.1

5-(Aziridin-3-yloxy)isoindoline-2-carboxylic acid tert-butyl ester(02450-1)



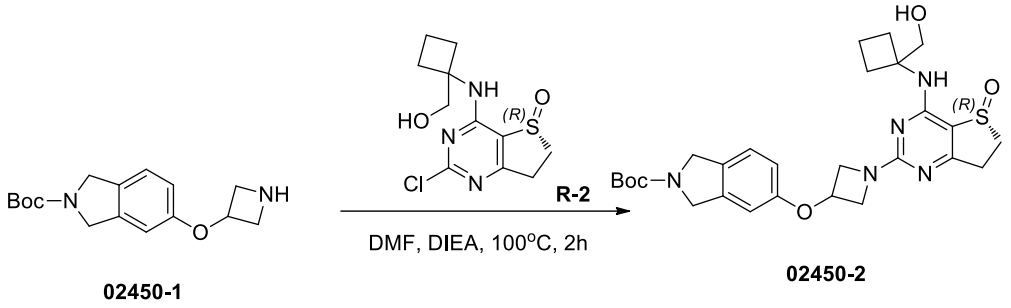
02450-0 **02450-1**

To a solution of 5-((1-((benzyloxycarbonyl)azetidin-3-yl)oxy)isindoline-2-carboxylic acid tert-butyl ester (200 mg, 0.47 mmol) in MeOH (3 mL) was added Pd/C (20 mg). The mixture was stirred under a hydrogen atmosphere at room temperature for 16 hours. After the reaction was complete, the mixture was filtered under reduced pressure, and the filtrate was concentrated in vacuo to afford the colorless oil (86 mg, 64% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{22}N_2O_3]$ $[M+H]^+$: 291.2; found: 291.4

2.2

(R)-5-((1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6, 7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)isoindoline-2-carboxylic acid tert-butyl ester(02450-2)

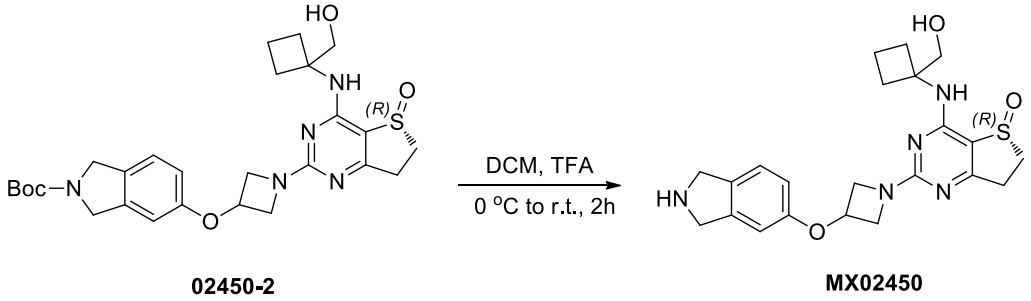


To a solution of 5-((azetidin-3-yl)oxy)isindoline-2-carboxylic acid tert-butyl ester (50 mg, 0.17 mmol) in DMF (2 mL) was added (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (49 mg, 0.17 mmol) and DIEA (65 mg, 0.51 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 2 hours until the starting material was consumed. The reaction mixture was concentrated in vacuo and the crude product was purified by column chromatography (MeOH/DCM=0/1 to 1/20, silica gel, 12 g, 20 mL/min, UV 254) to afford the yellow solid (87 mg, 86% yield).

ESI-MS *m/z* calcd for $[C_{27}H_{35}N_5O_5S]$ $[M+H]^+$: 542.2; found: 542.4

2.3

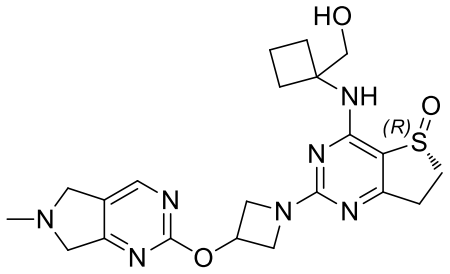
(R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(3-(isoindolin-5-yloxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02450)



To a solution of (R)-5-((1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)isindoline-2-carboxylic acid tert-butyl ester (30 mg, 0.05 mmol) in DCM (3 mL) at 0 °C under a nitrogen atmosphere was added TFA (0.6 mL). The mixture was stirred at room temperature for 2 hours, then concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the yellow solid (10.11 mg, 41% yield).

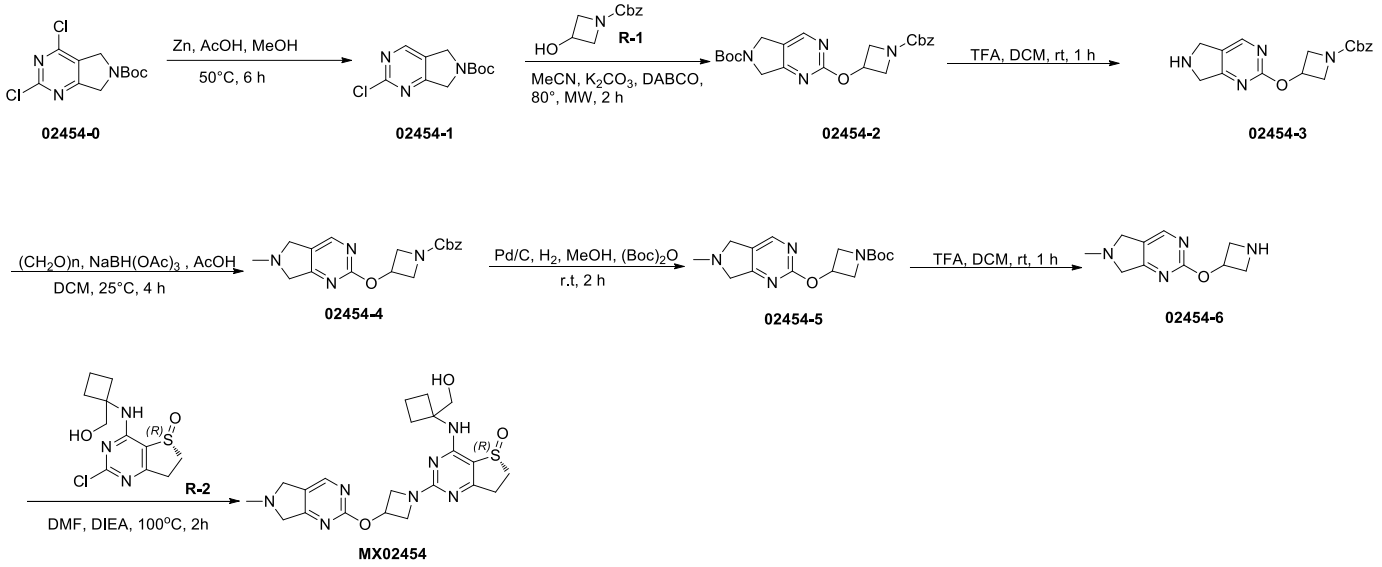
ESI-MS *m/z* calcd for $[C_{22}H_{27}N_5O_3S]$ $[M+H]^+$: 442.2; found: 441.6

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (s, 1H), 7.26 – 7.18 (m, 1H), 6.85 – 6.68 (m, 2H), 5.09 – 5.07 (m, 1H), 4.90 – 4.82 (m, 1H), 4.56 – 4.42 (m, 3H), 4.01 (d, *J* = 15.2 Hz, 2H), 3.96 – 3.84 (m, 2H), 3.73 – 3.66 (m, 2H), 3.45 – 3.38 (m, 2H), 3.25 – 3.17 (m, 2H), 2.97 – 2.85 (m, 2H), 2.37 – 2.24 (m, 2H), 2.15 – 2.10 (m, 2H), 1.79 – 1.68 (m, 2H).



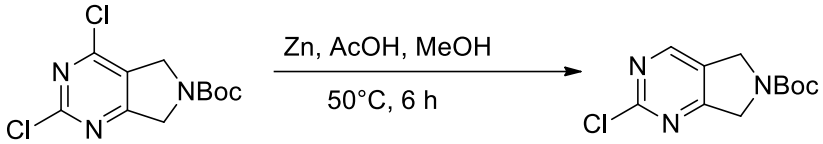
MX02454

1.Synthetic scheme:



2. Experimental section:

2.12-Chloro-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylic acid tert-butyl ester(02454-1)



02454-0 **02454-1**

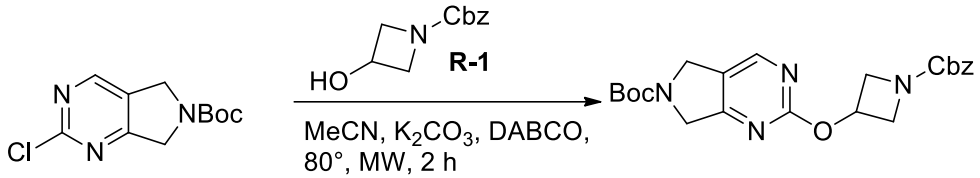
To a solution of 2,4-dichloro-5H-pyrrolo[3,4-d]pyrimidin-6(7H)-carboxylic acid tert-butyl ester (1 g, 3.46 mmol) and zinc powder (1.12 g, 17.30 mmol) in MeOH (10 mL) was

added acetic acid (1.04 g, 17.30 mmol). The mixture was stirred at 50 °C for 6 hours, then concentrated in vacuo. DCM (30 mL) was added, the mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0/1 to 1/4, silica gel, 40 g, 30 mL/min, UV 254) to afford the yellow solid (385 mg, 44% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{14}ClN_3O_2]$ $[M+H]^+$: 256.1; found: 256.3

2.2

2-((1-((Benzyloxy)carbonyl)azetidin-3-yl)oxy)-5H-pyrrolo[3,4-d]pyrimidine-6(7H)-carboxylic acid tert-butyl ester(02454-2)



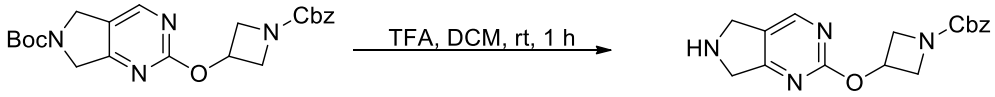
02454-1 **02454-2**

To a solution of 2,4-dichloro-5H-pyrrolo[3,4-d]pyrimidin-6(7H)-carboxylic acid tert-butyl ester (1 g, 3.46 mmol) and zinc powder (1.12 g, 17.30 mmol) in MeOH (10 mL) was added acetic acid (1.04 g, 17.30 mmol). The mixture was stirred at 50 °C for 6 hours, then concentrated in vacuo. DCM (30 mL) was added and the mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0/1 to 1/4, silica gel, 40 g, 30 mL/min, UV 254) to afford the yellow solid (385 mg, 44% yield).

ESI-MS *m/z* calcd for $[C_{22}H_{26}N_4O_5]$ $[M+H]^+$: 427.2; found: 426.8

2.3

3-((6,7-Dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)oxy)azetidine-1-carboxylic acid benzyl ester(02454-3)



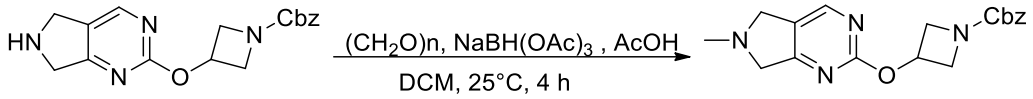
02454-2 **02454-3**

To a solution of 2-((1-((benzyloxycarbonyl)azetidin-3-yl)oxy)-5H-pyrrolo[3,4-d]pyrimidin-6(7H)-carboxylic acid tert-butyl ester (309 mg, 0.73 mmol) in DCM (5 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1 hour until the starting material was consumed. The mixture was concentrated in vacuo to afford the yellow oil (201 mg, 85% yield) which was used directly for the next step.

ESI-MS m/z calcd for $[C_{17}H_{18}N_4O_3]$ [M+H]+: 327.1; found: 327.0

2.4

3-((6-Methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)oxy)azetidine-1-carboxylic acid benzyl ester(02454-4)



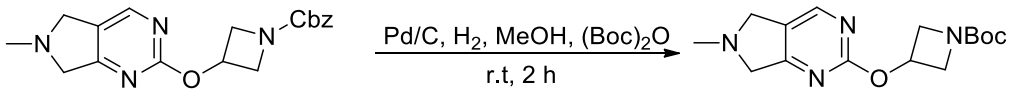
02454-3 **02454-4**

To a solution of 3-((6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)oxy)azetidine-1-carboxylic acid benzyl ester (201 mg, 0.62 mmol) and paraformaldehyde (92 mg, 3.08 mmol) in DCM (10 mL) at 0 °C was added sodium triacetoxyborohydride (394 mg, 1.86 mmol) in portions. The mixture was stirred under a nitrogen atmosphere at room temperature overnight. After the starting material was consumed, ice-water (15 mL) was added and the pH was adjusted to 9 with sodium bicarbonate. The mixture was extracted with DCM (30 mL) three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0/1 to 1/0, silica gel, 20 g, 30 mL/min, UV 254) to afford the yellow solid (34 mg, 16% yield).

ESI-MS *m/z* calcd for $[C_{18}H_{20}N_4O_3]$ $[M+H]^+$: 341.2; found: 341.2

2.5

tert-Butyl 3-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)oxy)azetidine-1-carboxylate(02454-5)



02454-4 **02454-5**

To a solution of 3-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)oxy)azetidine-1-carboxylic acid benzyl ester (34 mg, 0.10 mmol) in MeOH (3 mL) was added Pd/C (10 mg) and di-tert-butyl dicarbonate (44 mg, 0.20 mmol). The mixture was stirred under a hydrogen atmosphere at room temperature for 2 hours. After the starting material was consumed, the mixture was filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0/1 to 1/0, silica gel, 12 g, 30 mL/min, UV 254) to afford the yellow solid (18 mg, 59% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{22}N_4O_3]$ $[M+H]^+$: 307.2; found: 307.0

2.6

2-(Aziridin-3-yloxy)-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine(02454-6)



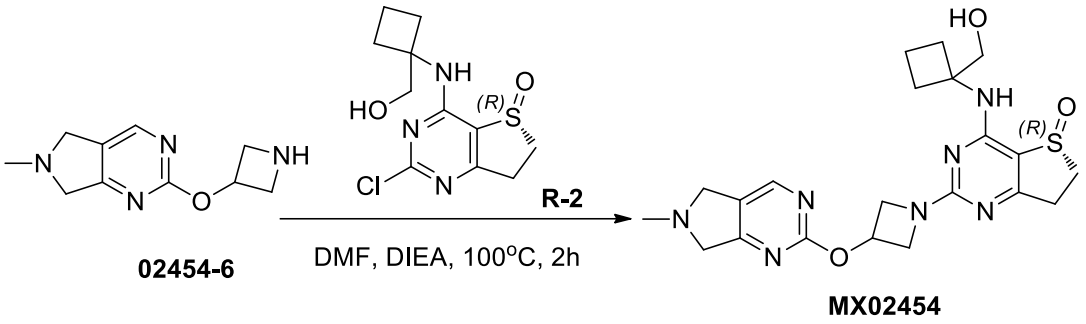
02454-5 **02454-6**

To a solution of 3-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (18 mg, 0.059 mmol) in DCM (2 mL) was added TFA (0.5 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 1 hour until the starting material was consumed and then the mixture was concentrated in vacuo to afford the white solid (10 mg, 83% yield) which was used directly for the next step.

ESI-MS *m/z* calcd for $[C_{10}H_{14}N_4O]$ $[M+H]^+$: 207.1; found: 207.3

2.7

(R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-2-(3-((6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)oxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02454)



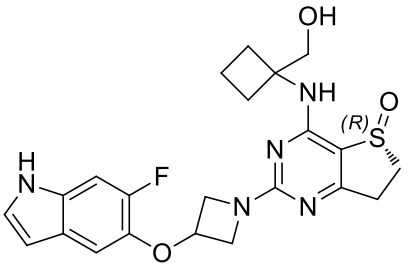
02454-6 **MX02454**

To a solution of 2-((azetidin-3-yl)oxy)-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine (10 mg, 0.049 mmol) in DMF (2 mL) was added (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (14 mg, 0.049 mmol) and DIEA (8.9 mg, 0.15 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 2 hours. After the reaction was complete, the mixture was concentrated in vacuo and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (5.68 mg, 26% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{27}N_7O_3S]$ $[M+H]^+$:458.2; found:457.9

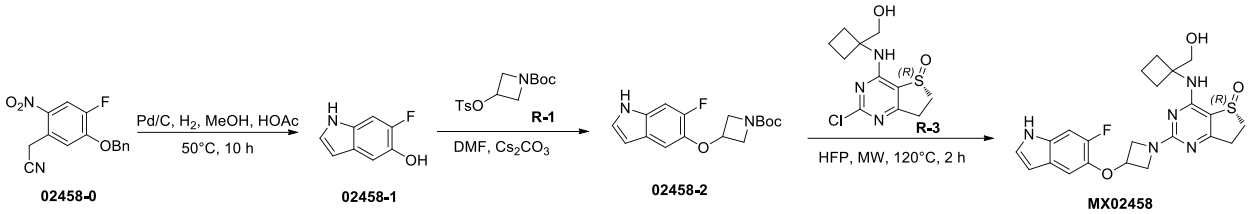
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.45 (s, 1H), 5.43 – 5.37 (m, 1H), 4.85 (t, *J* = 5.6 Hz, 1H)， 4.41 (dd, *J* = 10.4, 6.4 Hz, 2H)， 3.95 (d, *J* = 7.2 Hz, 2H)， 3.80 (d, *J* = 14.4 Hz, 4H)， 3.73 – 3.66 (m, 2H), 3.45 – 3.36 (m, 1H), 3.25 – 3.17 (m, 1H), 2.97 – 2.84 (m,

2H), 2.49 (s, 3H), 2.38 – 2.25 (m, 2H), 2.15 – 2.09 (m, 2H), 1.80 – 1.68 (m, 2H).



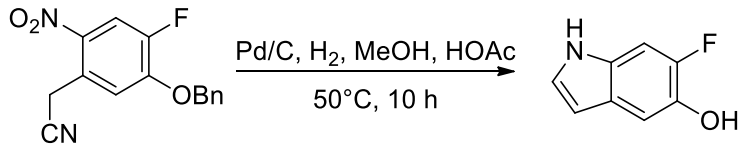
MX02458

1. Synthetic scheme:



2. Experimental section:

2.1 6-Fluoro-5-hydroxyindole(02458-1)



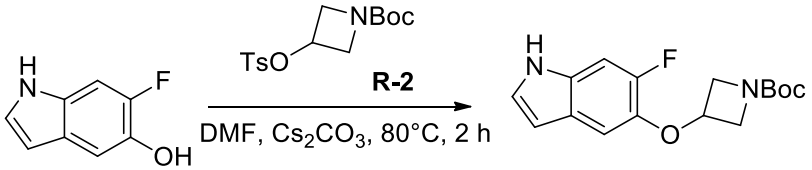
02458-0 **02458-1**

To a solution of 2-(5-(benzyloxy)-4-fluoro-2-nitrophenyl)acetonitrile (250 mg, 0.874 mmol) in MeOH (10 mL) and acetic acid (2 mL) was added Pd/C (25 mg). The mixture was stirred under a hydrogen atmosphere at 50 °C (3 MPa) for 10 hours. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to afford the colorless oil (98 mg, 74.24% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{19}FN_2O_3]$ $[M-H]^+$: 150.0; found: 150.2

2.2

tert-Butyl 3-((6-fluoro-1H-indol-5-yl)oxy)azetidine-1-carboxylate(02458-2)



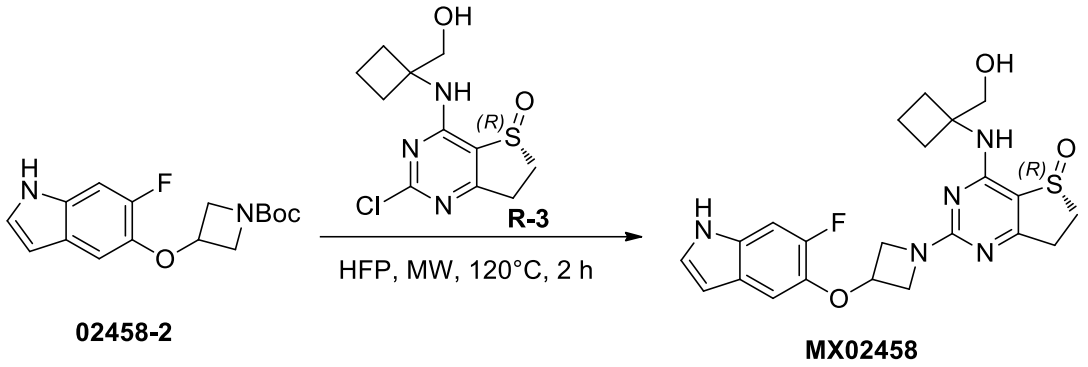
02458-1 **02458-2**

To a solution of 6-fluoro-5-hydroxyindole (80 mg, 0.529 mmol) in DMF (5 mL) and Cs_2CO_3 (517 mg, 1.59 mmol) was added 3-(p-toluenesulfonyloxy)azetidine-1-carboxylic acid tert-butyl ester (173 mg, 0.53 mmol). The reaction mixture was stirred at 80 °C for 2 hours, then concentrated in vacuo. Water (50 mL) was added, and the mixture was extracted with EA (30 mL) twice. The combined organic layers were washed with saturated brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE= 0 to 50%, silica gel, 12 g, 20 mL/min, UV 254) to afford the yellow oil (60 mg, 37.0% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{19}FN_2O_3]$ $[M-56+H]^+$: 251.1; found: 251.3

2.3

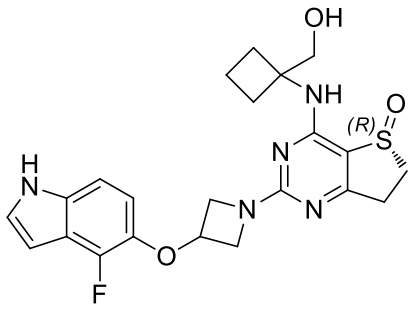
(R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(3-(isoindolin-5-yloxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02450)



To a solution of 3-((6-fluoro-1H-indol-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (50 mg, 0.16 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (46 mg, 0.16 mmol) in HFP (2 mL) was stirred under microwave conditions at 120 °C for 2 hours. After the reaction was complete, the mixture was concentrated in vacuo, and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (14.02 mg, 18.7% yield).

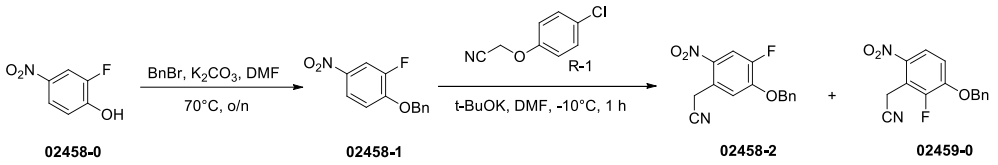
ESI-MS *m/z* calcd for $[C_{22}H_{24}FN_5O_3S]$ $[M+H]^+$: 458.2; found: 457.6

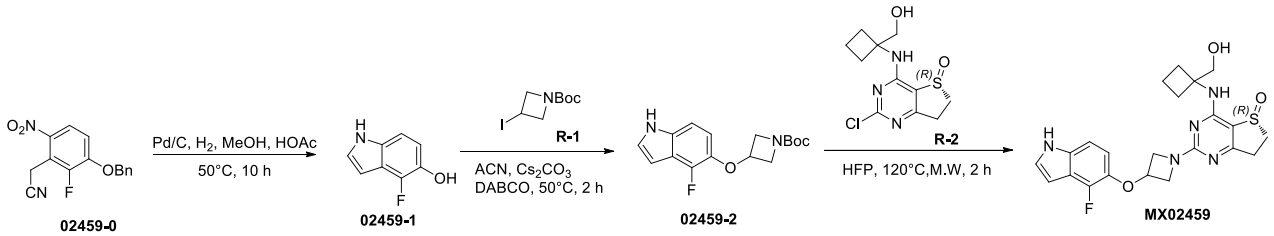
^1H NMR (400 MHz,DMSO-d_6) δ 11.04 (s, 1H), 7.46 (s, 1H), 7.31 (t, *J* = 2.8 Hz, 1H), 7.26 (d, *J* = 11.6 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.37 (t, *J* = 2.0 Hz, 1H), 5.15 – 5.10 (m, 1H), 4.85 (t, *J* = 6.0 Hz, 1H), 4.48 – 4.44 (m, 2H), 4.07 – 3.94 (m, 2H), 3.74 – 3.66 (m, 2H) , 3.46 – 3.37 (m, 1H), 3.25 –3.18 (m, 1H), 2.98 –2.65 (m, 2H), 2.38 –2.25 (m, 2H), 2.15 –2.10 (m, 2H), 1.82 –1.68 (m, 2H).



MX02459

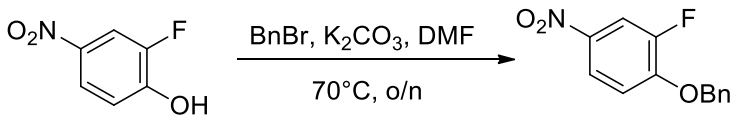
1. Synthetic scheme:





2. Experimental section:

2.1 1-Benzyloxy-2-fluoro-4-nitrobenzene(02458-0)



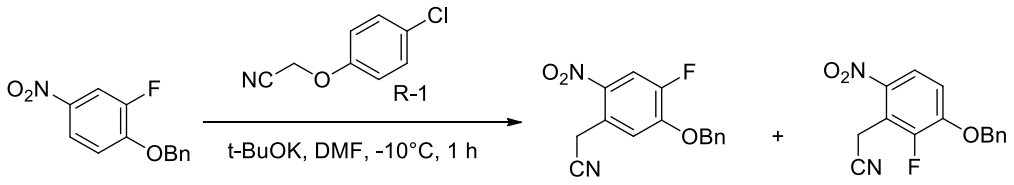
02458-0 **02458-1**

To a solution of 2-fluoro-4-nitrophenol (10 g, 63.69 mmol) in DMF (50 mL) was added potassium carbonate (17.58 g, 127.38 mmol) and benzyl bromide (16.34 g, 95.53 mmol). The mixture was stirred at 70 °C overnight. After cooling, ice-water (60 mL) was added. The precipitated white solid was filtered and concentrated to dryness to afford the white solid (15.2 g, 97% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 – 8.12 (m, 2H), 7.53 – 7.36 (m, 6H), 5.36 (s, 2H).

2.2

2-(5-(Benzyloxy)-4-fluoro-2-nitrophenyl)acetonitrile (02458-2) and 2-(3-(Benzyloxy)-2-fluoro-6-nitrophenyl)acetonitrile（02459-0）

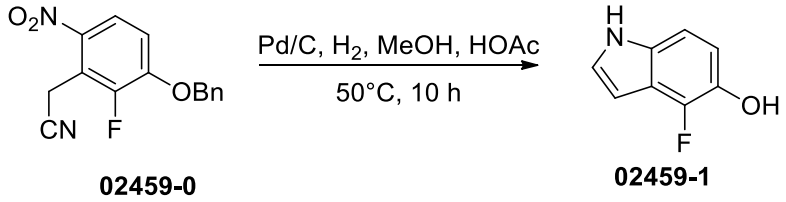


To a solution of 1-benzyloxy-2-fluoro-4-nitrobenzene (6 g, 24.29 mmol) in DMF (30 mL) at -10 °C was added potassium tert-butyloxide (t-BuOK, 2.72 g, 24.29 mmol) and 2-(4-chlorophenoxy)acetonitrile (4.05 g, 24.29 mmol). The mixture was stirred at -10 °C for 1 hour. Ice-water (50 mL) was added to the reaction mixture and the mixture was extracted with EA (50 mL) twice. The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE=0 to 1, silica gel, 80 g, 50 mL/min, UV 254) to afford the yellow solid 2-(5-(benzyloxy)-4-fluoro-2-nitrophenyl)acetonitrile (1.35 g, 19% yield) and the yellow solid 2-(3-(benzyloxy)-2-fluoro-6-nitrophenyl)acetonitrile (1.10 g, 16% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{11}FN_2O_3]$ $[M+18]^+$:304.1; found: 304.2 (02458-2)

ESI-MS *m/z* calcd for $[C_{15}H_{11}FN_2O_3]$ $[M+18]^+$:304.1; found: 304.2 (02459-0)

2.3 4-Fluoro-1H-indol-5-ol (02459-1)

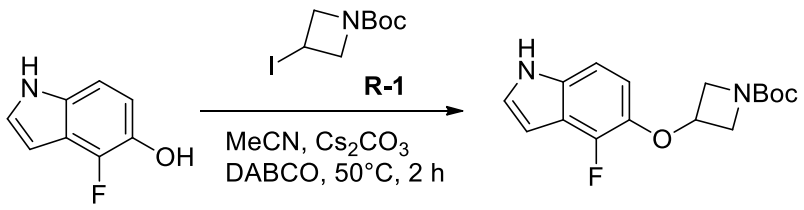


To a solution of 2-(3-(benzyloxy)-2-fluoro-6-nitrophenyl)acetonitrile (600 mg, 2.09 mmol) in MeOH/HOAc (v/v=9/1, 10 mL) was added Pd/C (60 mg). The reaction mixture was stirred under a hydrogen atmosphere at 3 MPa and 50 °C for 10 hours until the starting material was consumed. The mixture was filtered and concentrated to dryness in vacuo. The crude product was purified by column chromatography (EA/PE = 0 to 1, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (200 mg, 63% yield).

ESI-MS *m/z* calcd for $[C_8H_6FNO]$ $[M+H]^+$: 152.0; found: 151.2

2.4

tert-Butyl 3-((4-fluoro-1H-indol-5-yl)oxy)azetidine-1-carboxylate (02459-2)



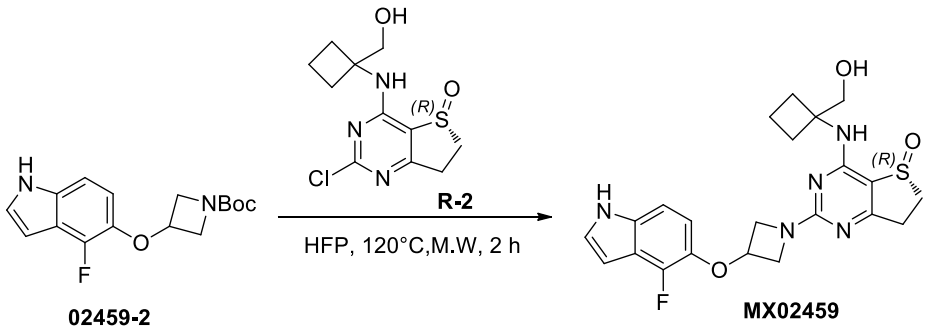
02459-1 02459-2

To a solution of 4-fluoro-1H-indol-5-ol (100 mg, 0.66 mmol) in MeCN (4 mL) was added 3-iodoazetidine-1-carboxylic acid tert-butyl ester (187 mg, 0.66 mmol), Cs_2CO_3 (322 mg, 0.99 mmol) and DABCO (7 mg, 0.066 mmol). The mixture was stirred at 50 °C for 2 hours. After the starting material was consumed, the reaction mixture was adjusted to pH 6 with 1N HCl aqueous solution and extracted with EA (20 mL) three times. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0 to 1, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow oil (41 mg, 20% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{19}FN_2O_3]$ $[M-56+H]^+$: 251.1; found: 251.0

2.5

(R)-2-(3-((4-Fluoro-1H-indol-5-yl)oxy)azetidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5 -oxide(MX02459)



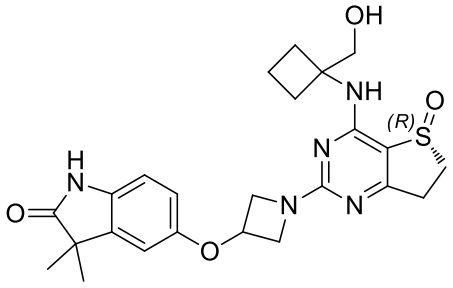
02459-2 MX02459

To a solution of 3-((4-fluoro-1H-indol-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (20 mg, 0.08 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (23 mg, 0.08 mmol) in HFP (2 mL) was stirred under microwave conditions at 120 °C for 2 hours. After the reaction was complete, the mixture was concentrated in vacuo and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (4.31 mg, 12% yield).

ESI-MS *m/z* calcd for $[C_{22}H_{24}FN_5O_3S]$ $[M+H]^+$: 458.2; found: 457.7

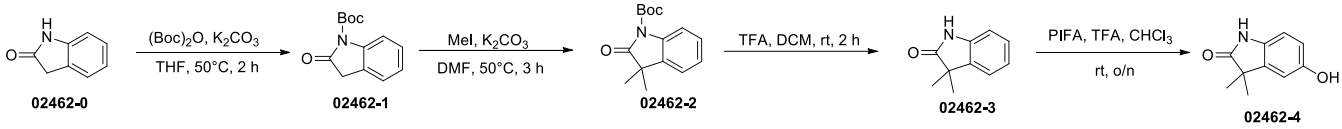
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 7.45 (s, 1H), 7.38 (t, J = 2.8 Hz, 1H),

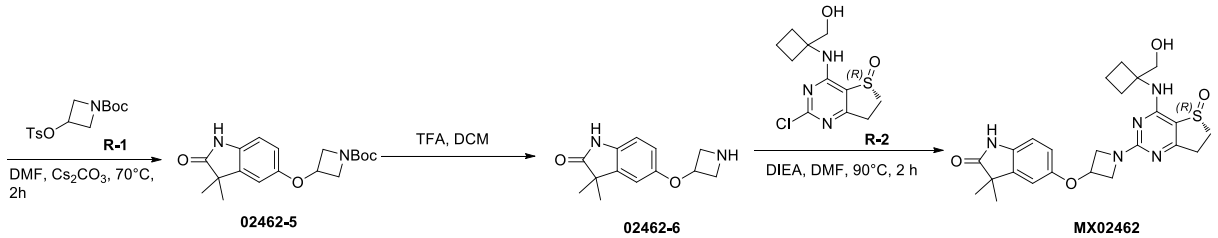
7.16 (d, *J* = 8.8 Hz, 1H), 6.87 (t, *J* = 8.4 Hz, 1H), 6.46 – 6.45 (m, 1H), 5.12 – 5.07 (m, 1H), 4.85 (t, *J* = 5.6 Hz, 1H), 4.40 – 4.36 (m, 2H), 4.02 – 4.00 (m, 2H), 3.71 – 3.66 (m, 2H), 3.45 – 3.37 (m, 1H), 3.29 – 3.20 (m, 1H), 2.97 – 2.85 (m, 2H), 2.39 – 2.26 (m, 2H), 2.15 – 2.10 (m, 2H), 1.80 – 1.68 (m, 2H).



MX02462

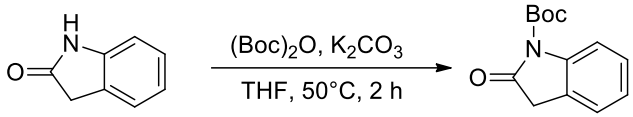
1. Synthetic scheme:





2. Experimental section:

2.1 tert-Butyl 2-oxoindolin-1-carboxylate(02462-1)

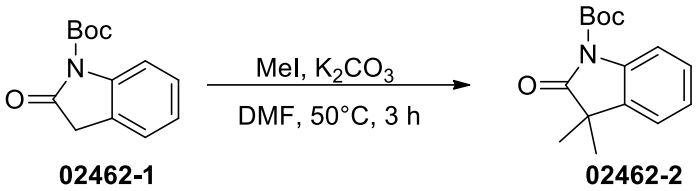


02462-0 **02462-1**

To a solution of indolin-2-one (3 g, 22.5 mmol) in THF (50 mL) at room temperature was added K_2CO_3 (31 g, 225.0 mmol) and di-tert-butyl dicarbonate (7.37 g, 33.83 mmol). The mixture was stirred at 50 °C for 2 hours. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. The crude product was extracted with saturated aqueous $NaHCO_3$ (40 mL) and EA (40 mL) twice. The combined organic layers were washed with saturated brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE= 0 to 1, silica gel, 80 g, 50 mL/min, UV 254) to afford the colorless oil (2.67 g, 51% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{15}NO_3]$ $[M-56+H]^+$: 178.1; found: 178.1

2.2 tert-Butyl 3,3-dimethyl-2-oxoindolin-1-carboxylate (02462-2)

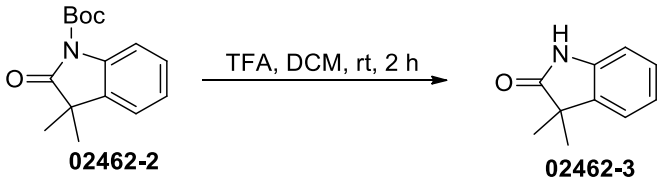


02462-1 **02462-2**

To a solution of tert-butyl 2-oxoindoline-1-carboxylate (2.67 g, 11.46 mmol) in DMF (20 mL) was added potassium carbonate (4.74 g, 34.38 mmol) and methyl iodide (4.07 g, 28.65 mmol). The mixture was stirred at 50 °C for 3 hours. After cooling, water (40 mL) was added and the mixture was extracted with EA (40 mL) twice. The combined organic layers were washed with saturated brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0 to 1, silica gel, 40 g, 40 mL/min, UV 254) to afford the yellow oil (1.88 g, 63% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{19}NO_3]$ $[M-56+H]^+$: 206.1; found: 206.4

2.3 3,3-Dimethylindolin-2-one (02462-3)

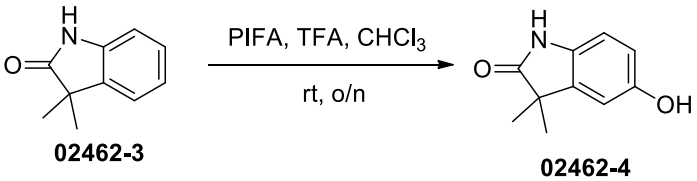


02462-2 **02462-3**

To a solution of 3,3-dimethyl-2-oxoindoline-1-carboxylic acid tert-butyl ester (1.88 g, 7.20 mmol) in DCM (10 mL) was added TFA (1 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 2 hours until the starting material was consumed. The mixture was concentrated in vacuo to afford the yellow oil (1.08 g, 94% yield).

ESI-MS *m/z* calcd for $[C_{10}H_{11}NO]$ $[M+H]^+$: 162.1; found: 162.4

2.4 5-Hydroxy-3,3-dimethylindolin-2-one (02462-4)



02462-3 **02462-4**

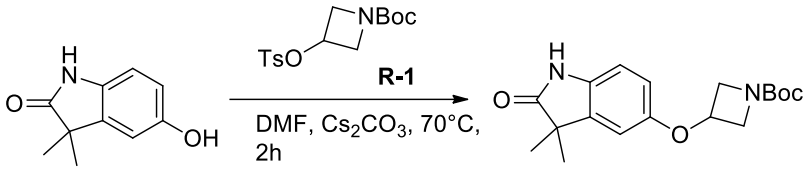
To a solution of 3,3-dimethylindolin-2-one (1.08 g, 6.71 mmol) in $CHCl_3$ (20 mL) was added TFA (7.65 g, 67.1 mmol) and PIFA (3.46 g, 8.05 mmol). The mixture was stirred at room temperature overnight. After the starting material was consumed, the reaction mixture was adjusted to pH 8 with saturated aqueous $NaHCO_3$ solution and extracted with EA (40 mL) three times. The combined organic layers were washed with saturated brine (40 mL), dried over

anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0 to 1, silica gel, 40 g, 40 mL/min, UV 254) to afford the yellow solid (471 mg, 39% yield).

ESI-MS *m/z* calcd for $[C_{10}H_{11}NO_2]$ $[M+H]^+$: 178.1; found: 178.2

2.5

tert-Butyl 3-((3,3-dimethyl-2-oxoindolin-5-yl)oxy)azetidine-1-carboxylate (02462-5)

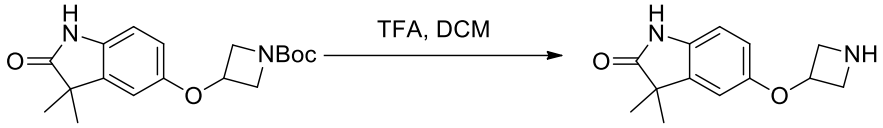


02462-4 **02462-5**

To a solution of 5-hydroxy-3,3-dimethylindolin-2-one (61 mg, 0.34 mmol) and 3-(p-toluenesulfonyloxy)azetidine-1-carboxylic acid tert-butyl ester (114 mg, 0.34 mmol) in DMF (3 mL) at room temperature was added Cs_2CO_3 (222 mg, 0.68 mmol). The mixture was stirred at 70 °C for 2 hours. Water (20 mL) was added, and the mixture was extracted with EA (40 mL) twice. The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/DCM =0 to 1, silica gel, 12 g, 30 mL/min, UV 254) to afford the yellow solid (43 mg, 38% yield).

ESI-MS *m/z* calcd for $[C_{18}H_{24}N_2O_4]$ $[M-56+H]^+$: 277.2; found: 277.4

2.6 5-(Azetidin-3-yloxy)-3,3-dimethylindolin-2-one (02462-6)



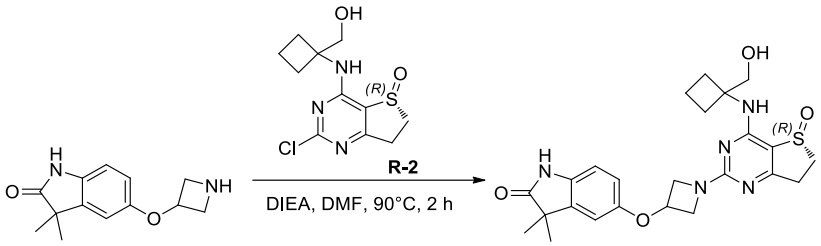
02462-5 **02462-6**

To a solution of 3-((3,3-dimethyl-2-oxoindolin-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (43 mg, 0.13 mmol) in DCM (2 mL) was added TFA (0.2 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1 hour until the starting material was consumed. The mixture was concentrated in vacuo to afford the yellow oil (25 mg, 83% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{16}N_2O_2]$ $[M+H]^+$: 233.1; found: 233.2

2.7

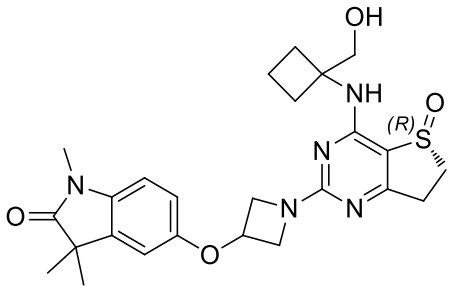
(R)-5-((1-(4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)-3, 3,3-dimethylindolin-2-one (MX02462)



To a solution of 5-(azetidin-3-yl oxide)-3,3-dimethylindolin-2-one (25 mg, 0.11 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (31 mg, 0.11 mmol) in DMF (2 mL) was added DIEA (43 mg, 0.33 mmol). The mixture was stirred at 90 °C for 2 hours, cooled to room temperature and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (25.91 mg, 50% yield).

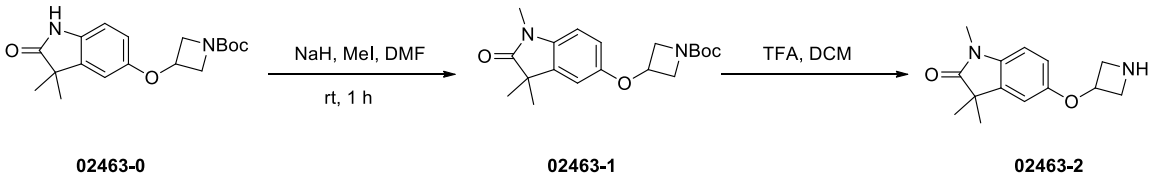
ESI-MS *m/z* calcd for $[C_{24}H_{29}N_5O_4S]$ $[M+H]^+$: 484.2; found: 484.3

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.45 (s, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.34 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.06 – 5.01 (m, 1H), 4.85 (t, *J* = 5.6 Hz, 1H), 4.45 – 4.41 (m, 2H), 3.91 – 3.89 (m, 2H), 3.73 – 3.59 (m, 2H), 3.45 – 3.36 (m, 1H), 3.25 – 3.18 (m, 1H), 2.96 – 2.84 (m, 2H), 2.39 – 2.26 (m, 2H), 2.15 – 2.08 (m, 2H), 1.83 – 1.68 (m, 2H), 1.24 (s, 6H).

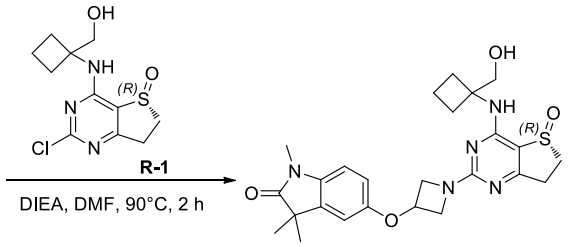


MX02463

1. Synthetic scheme:



02463-0 02463-1 02463-2

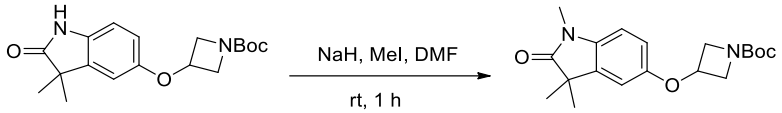


MX02463

2. Experimental section:

2.1

tert-Butyl 3-((1,3,3-trimethyl-2-oxoindolin-5-yl)oxy)azetidine-1-carboxylate (02463-1)



02463-0 02463-1

To a solution of 3-((3,3-dimethyl-2-oxoindolin-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (80 mg, 0.24 mmol) in DMF (2 mL) was added NaH (60%, 15 mg, 0.36 mmol). The mixture was stirred at 0 °C for 30 minutes, followed by the addition of MeI (30 mg, 0.24 mmol) and then stirred at room temperature for 1 hour. Water (15 mL) was added and the mixture was extracted with EA (15 mL) twice. The combined organic layers were washed with saturated brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE 0 to 10%, silica gel, 20 g, 20 mL/min, UV 254) to afford the colorless oil (48 mg, 58% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{26}N_2O_4]$ $[M+H]^+$: 347.2; found: 347.4

2.2 5-(Azetidin-3-yloxy)-1,3,3-trimethylindolin-2-one(02463-2)



02463-1 02463-2

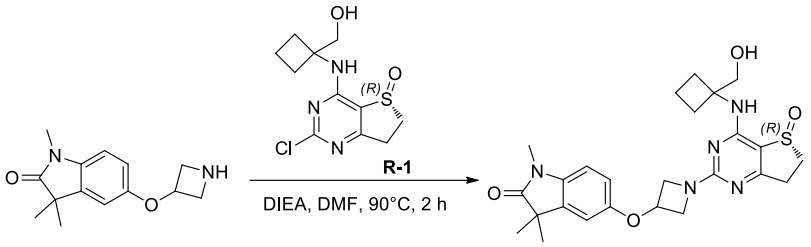
To a solution of 3-((1,3,3-trimethyl-2-oxoindolin-5-yl)oxy)azetidine-1-carboxylic acid

tert-butyl ester (48 mg, 0.13 mmol) in DCM (2 mL) was added TFA (0.2 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1 hour until the starting material was consumed. The mixture was concentrated in vacuo to afford the yellow oil (23 mg, 68% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{18}N_2O_2]$ $[M+H]^+$: 247.1; found: 247.4

2.3

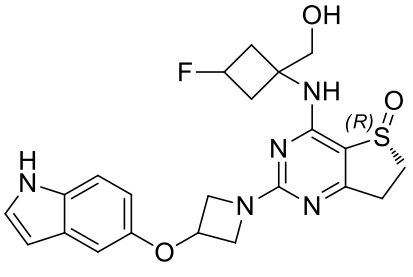
(R)-5-((1-(4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)-1,3, 3-trimethylindolin-2-one(MX02463)



To a solution of 5-(azetidin-3-yl oxide)-1,3,3-trimethylindolin-2-one (23 mg, 0.09 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (27 mg, 0.09 mmol) in DMF (2 mL) was added DIEA (37 mg, 0.27 mmol). The mixture was stirred at 90 °C for 2 hours, cooled to room temperature and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (11.03 mg, 24% yield).

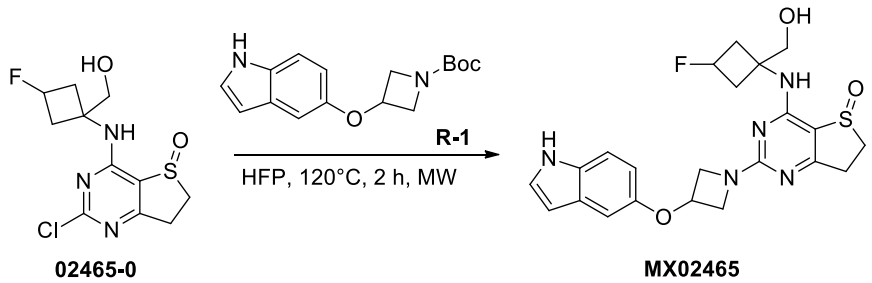
ESI-MS *m/z* calcd for $[C_{25}H_{31}N_5O_4S]$ $[M+H]^+$: 498.2; found: 497.6

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (s, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.74 (dd, J = 8.4, 2.8 Hz, 1H), 5.10 – 5.05 (m, 1H), 4.85 (t, J = 5.6 Hz, 1H), 4.47 – 4.43 (m, 2H), 3.91 – 3.89 (m, 2H), 3.70 – 3.67 (m, 2H), 3.45 – 3.37 (m, 1H), 3.25 – 3.18 (m, 1H),3.10 (s, 3H), 2.96 – 2.84 (m, 2H), 2.50 – 2.26 (m, 2H), 2.15 – 2.10 (m, 2H), 1.79 – 1.68 (m, 2H), 1.26 (s, 6H).



MX02465

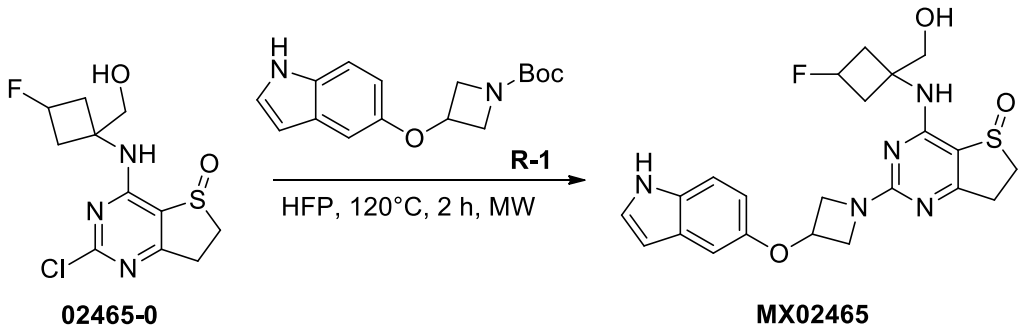
1. Synthetic scheme:



2. Experimental section:

2.1

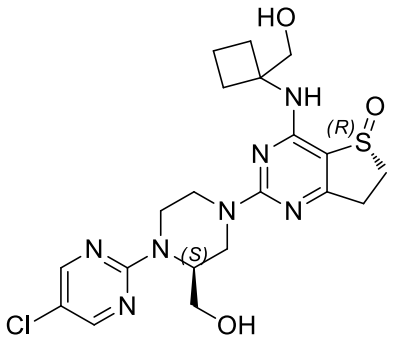
2-(3-((1H-indol-5-yl)oxy)azetidin-1-yl)-4-((3-fluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02465)



To a solution of 2-chloro-4-((3-fluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (20 mg, 0.065 mmol) and 3-((1H-indol-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (18.8 mg, 0.065 mmol) in HFP (3 mL) was stirred under microwave conditions at 120 °C for 2 hours. Water (10 mL) was added to the mixture and it was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid compound (15.0 mg, 50.1% yield).

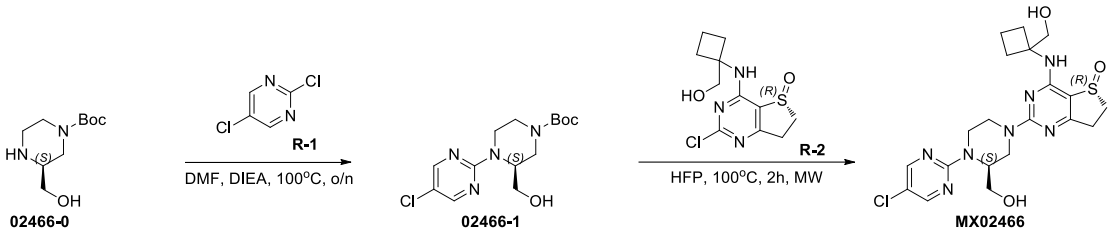
ESI-MS *m/z* calcd for $[C_{22}H_{24}FN_5O_3S]$ $[M+H]^+$: 458.2; found: 458.4

^{1}H NMR (400 MHz,DMSO-d_6) δ 10.97 (s, 1H), 7.89 – 7.54 (m, 1H), 7.32 – 7.30 (m, 2H), 6.93 (s, 1H), 6.72 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.35 (s, 1H), 5.20 – 4.83 (m, 3H), 4.48 – 4.44 (m, 2H), 4.03 – 3.89 (m, 2H), 3.65 (d, *J* = 6.0 Hz, 1H), 3.53 (d, *J* = 5.6 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.24 – 3.17 (m, 1H), 2.98 –2.73 (m, 4H)，2.46 –2.31 (m, 2H).



MX02466

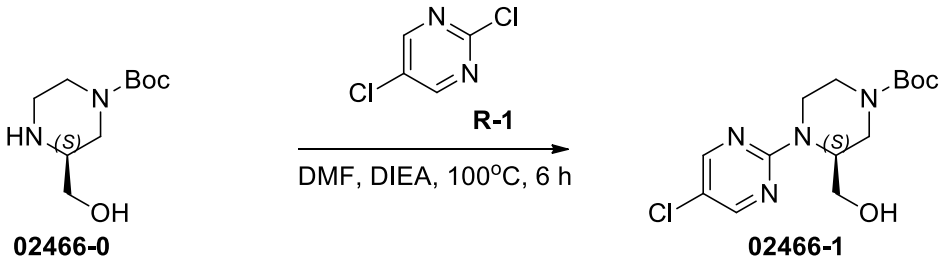
1. Synthetic scheme:



2. Experimental section:

2.1

(S)-4-(5-Chloropyrimidin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylic acid tert-butyl ester(02466-1)

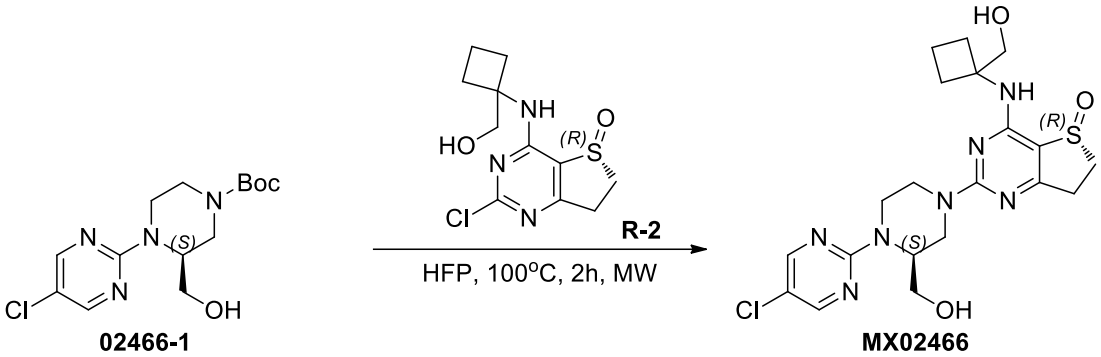


To a solution of (S)-3-(hydroxymethyl)piperazine-1-carboxylic acid tert-butyl ester (250 mg, 1.16 mmol) in DMF (10 mL) was added 2,5-dichloropyrimidine (171 mg, 1.16 mmol) and DIEA (449 mg, 3.48 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C for 6 hours until the starting material was consumed. Water (20 mL) was added, and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0/1 to 2/3, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow oil (180 mg, 47% yield).

ESI-MS m/z calcd for $[C_{14}H_{21}ClN_4O_3]$ $[M+H]^+$: 329.1; found: 329.3

2.2

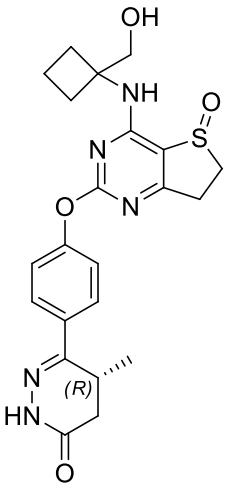
(R)-2-((S)-4-(5-chloropyrimidin-2-yl)-3- (hydroxymethyl)piperazin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02012)



To a solution of (S)-4-(5-chloropyrimidin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxylic acid tert-butyl ester (40 mg, 0.12 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (34 mg, 0.12 mmol) in HFP (2 mL) was stirred under microwave conditions at 120 °C for 2 hours. After the reaction was complete, the mixture was concentrated in vacuo and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (14.41 mg, 25% yield).

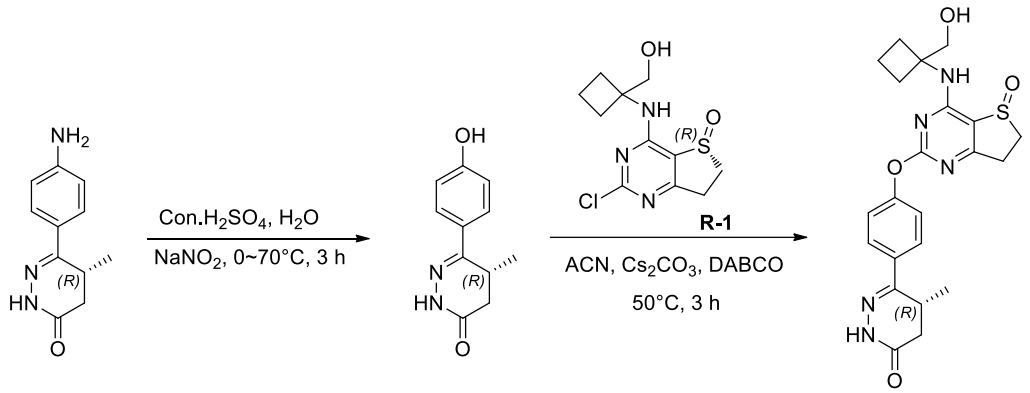
ESI-MS *m/z* calcd for $[C_{20}H_{26}ClN_7O_3S]$ $[M+H]^+$: 480.2; found: 480.2

^1H NMR (400 MHz,DMSO-d_6) δ 8.44 (s, 2H), 7.36 (s, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 4.74 (t, *J* = 5.2 Hz, 1H), 4.70 – 4.38 (m, 4H), 3.76 – 3.68 (m, 2H), 3.48 – 3.37 (m, 3H), 3.30 – 3.18 (m, 4H), 2.96 – 2.84 (m, 2H), 2.41 – 2.30 (m, 2H), 2.23 – 2.11 (m, 2H), 1.84 –1.70 (m, 2H).



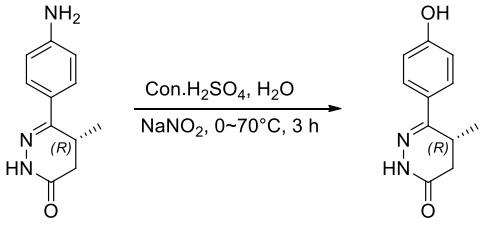
MX02472-rac

1. Synthetic scheme:



2. Experimental section:

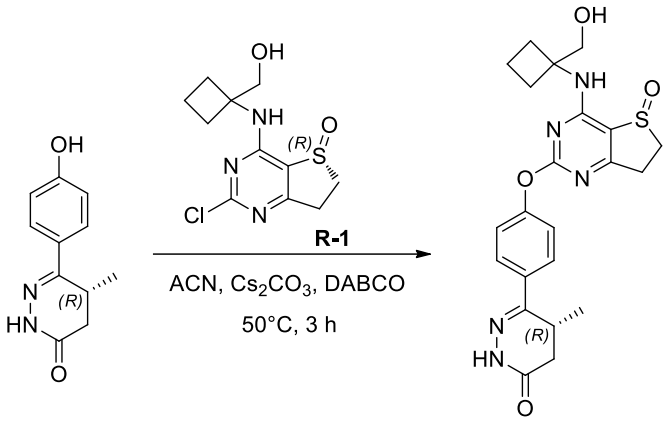
2.1(R)-6-(4-Hydroxyphenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one(02472-1)



To a solution of (R)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazine-3(2H)-one (100 mg, 0.49 mmol) in water (2 mL) at 0 °C was added sulfuric acid (200 mg, 2.04 mmol). The mixture was stirred at 0 °C and a sodium nitrite aqueous solution (1 mL, 38 mg, 0.55 mmol) was slowly added dropwise to the reaction mixture. The mixture was stirred for 20 minutes and then slowly heated to 70 °C over 20 minutes and stirred for 3 hours. The reaction mixture was poured into water (10 mL), filtered and dried to afford the crude product. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the dark brown solid (38 mg, 38% yield).

2.2

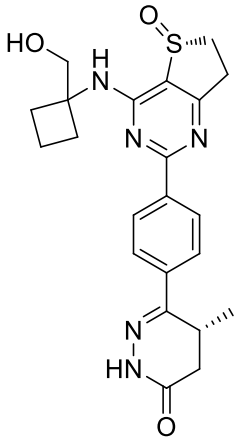
(5R)-6-(4-((4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)oxy)phenyl)-5-methyl-4,5-dihydropyridazine-3 (2H)-one (MX02472-rac)



To a solution of (R)-6-(4-hydroxyphenyl)-5-methyl-4,5-dihydropyridazine-3(2H)-one (25 mg, 0.12 mmol) in MeCN (2 mL) was added (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (34 mg, 0.12 mmol), Cs_2CO_3 (47 mg, 0.14 mmol) and DABCO (1 mg, 0.012 mmol). The mixture was stirred under a nitrogen atmosphere at 50 °C for 3 hours. After the starting material was consumed, water (10 mL) was added, and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (6.15 mg, 11% yield).

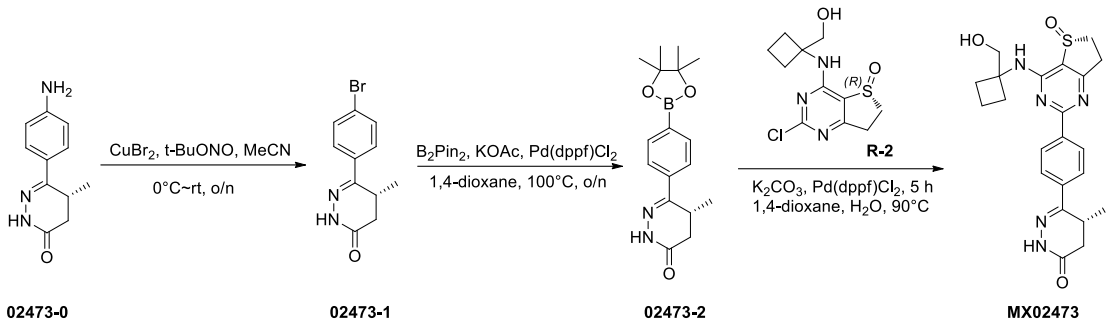
ESI-MS *m/z* calcd for $[C_{22}H_{25}N_5O_4S]$ $[M+H]^+$: 456.2; found: 455.6

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.11 (s, 1H), 7.84– 7.82 (m, 2H), 7.20 – 7.18 (m, 2H), 4.75 – 4.73 (m, 1H), 3.57 – 3.36 (m, 5H), 3.10 – 2.96 (m, 2H), 2.76 – 2.27 (m, 1H), 2.32 – 2.28 (m, 1H), 2.24 – 2.01 (m, 2H), 1.77 – 1.66 (m, 2H), 1.52 – 1.43 (m, 2H), 1.06 (d, *J* = 7.2, 3H).



MX02473

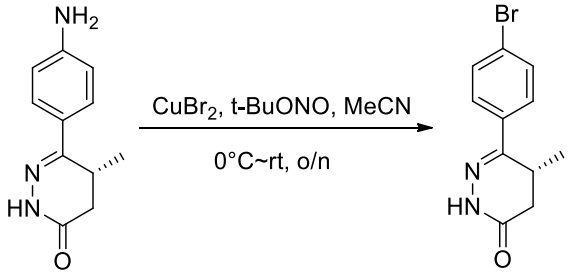
1. Synthetic scheme:



2. Experimental section:

2.1

(R)-6-(4-Bromophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one(02473-1)



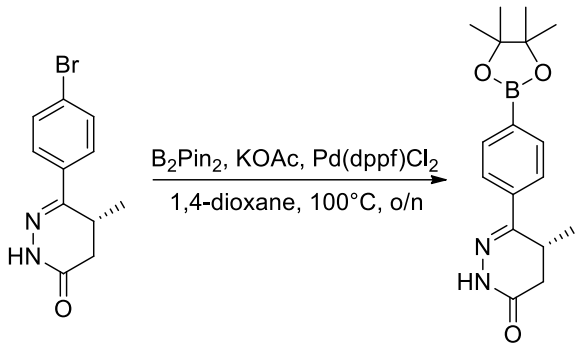
02473-0 **02473-1**

To a solution of (R)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazine-3(2H)-one (100 mg, 0.49 mmol) in MeCN (3 mL) at 0 °C was added $CuBr_2$ (110 mg, 0.49 mmol) and t-BuONO (75 mg, 0.74 mmol). The mixture was stirred at room temperature under a nitrogen atmosphere overnight. Water (20 mL) was added to the reaction mixture and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0 to 1, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (87 mg, 66% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{11}BrN_2O]$ $[M+H]^+$: 267.0; found: 267.1

2.2

(R)-6-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one(02473-2)



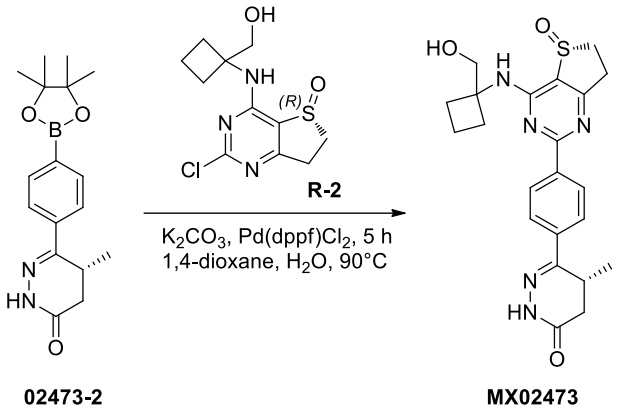
02473-1 **02473-2**

To a solution of (R)-6-(4-bromophenyl)-5-methyl-4,5-dihydropyridazine-3(2H)-one (87 mg, 0.32 mmol) in 1,4-dioxane (2 mL) was added B2Pin2 (813 mg, 3.2 mmol), KOAc (94 mg, 0.96 mmol) and Pd(dppf)Cl_2 (22 mg, 0.032 mmol). The mixture was stirred under a nitrogen atmosphere at 100 °C overnight. After the starting material was consumed, the reaction mixture was cooled and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0/1 to 1/1, silica gel, 40 g, 30 mL/min, UV 254) to afford the yellow solid (42 mg, 41% yield).

ESI-MS *m/z* calcd for $[C_{17}H_{23}BN_2O_3]$ $[M+H]^+$: 315.2; found: 315.0

2.3

(R)-6-(4-((R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)phenyl)-5-methyl-4,5-dihydropyridazine-3 (2H)-one (MX02473)



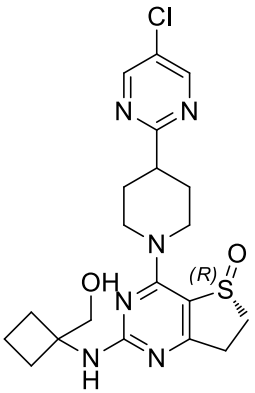
02473-2 **MX02473**

To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (29 mg, 0.10 mmol) in 1,4-dioxane/water (2.5 mL, v/v = 4/1) was added (R)-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl)-5-methyl-4,5-dihydropyridazine-3(2H)-one (32 mg, 0.10 mmol), K_2CO_3 (41 mg, 0.30 mmol) and Pd(dppf)Cl_2 (7 mg, 0.01 mmol). The mixture was stirred under a nitrogen atmosphere at 90 °C for 5 hours until the starting material was consumed. Water (20 mL) was added, and the mixture

was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (13.21 mg, 30% yield).

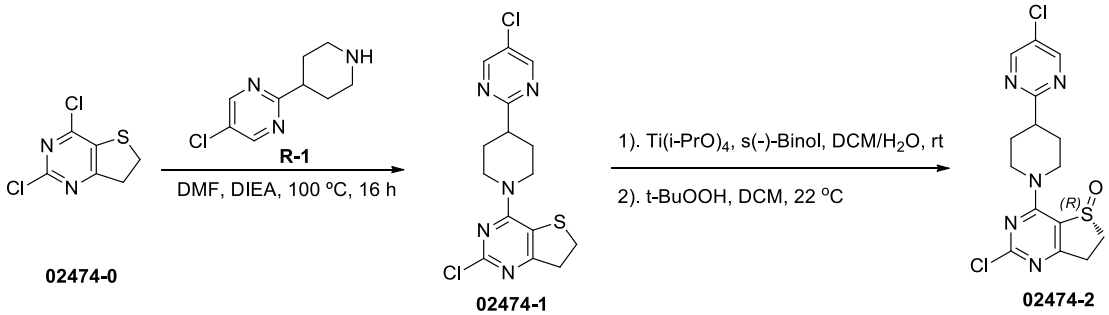
ESI-MS *m/z* calcd for $[C_{22}H_{25}N_5O_3S]$ $[M+H]^+$: 440.2; found: 439.6

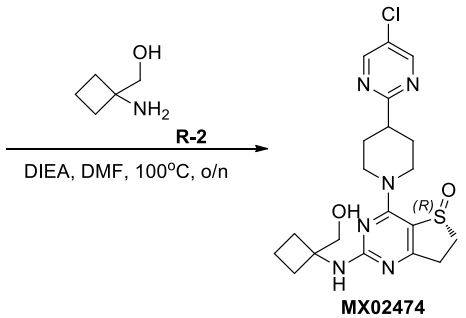
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.37 (d, *J* = 8.4 Hz, 2H), 8.08 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 4.93 (t, *J* = 6.0 Hz, 1H), 3.87 – 3.81 (m, 2H), 3.69 – 3.61 (m, 1H), 3.47 – 3.36 (m, 2H), 3.26 – 3.20 (m, 1H), 3.06 – 3.01 (m, 1H), 2.77 – 2.71 (m, 1H), 2.50 – 2.25 (m, 5H), 1.88 – 1.82 (m, 2H), 1.11 (d, *J* = 7.2 Hz, 3H).



MX02474

1. Synthetic scheme:

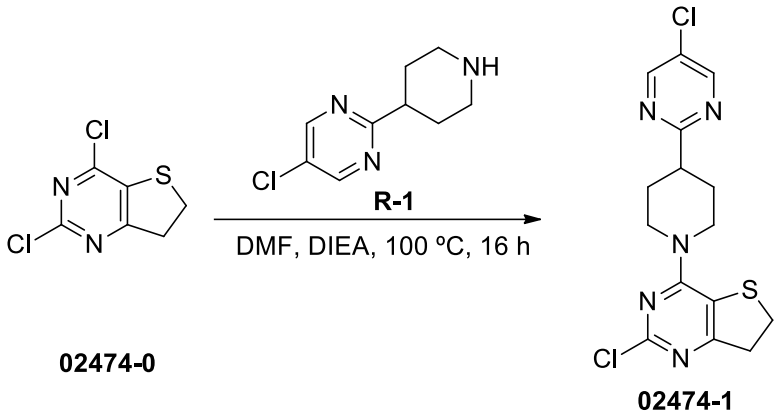




2. Experimental section:

2.1

2-Chloro-4-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine(02474-1)

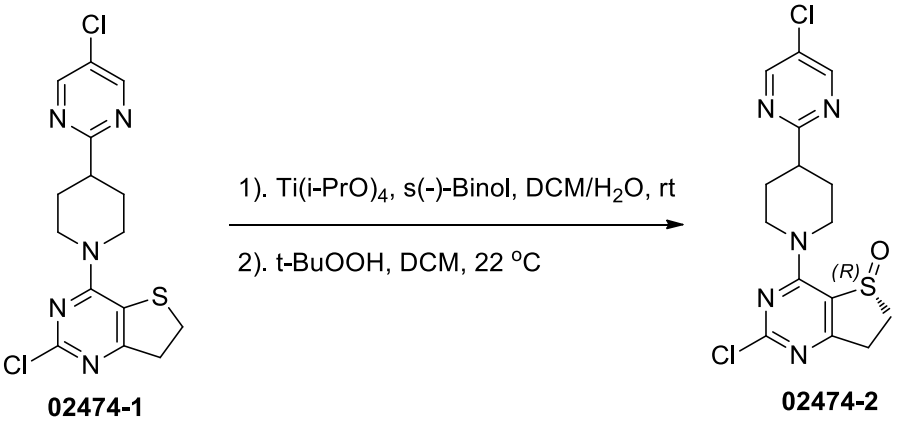


To a solution of 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidine (50.0 mg, 0.241 mmol) in DMF (4.0 mL) was added 5-chloro-2-(piperidin-4-yl)pyrimidine (48.0 mg, 0.241 mmol) and DIEA (0.5 mL). The mixture was stirred at 100 °C for 16 hours, then concentrated in vacuo. Water (10 mL) was added, and the mixture was extracted with DCM (10 mL) three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE= 0 to 100%, silica gel, 20 g, 30 mL/min, UV 254) to afford the yellow solid (45.0 mg, 50.6% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{15}Cl_2N_5S]$ $[M+H]^+$: 368.1; found: 368.2

2.2

(R)-2-Chloro-4-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(02474-2)



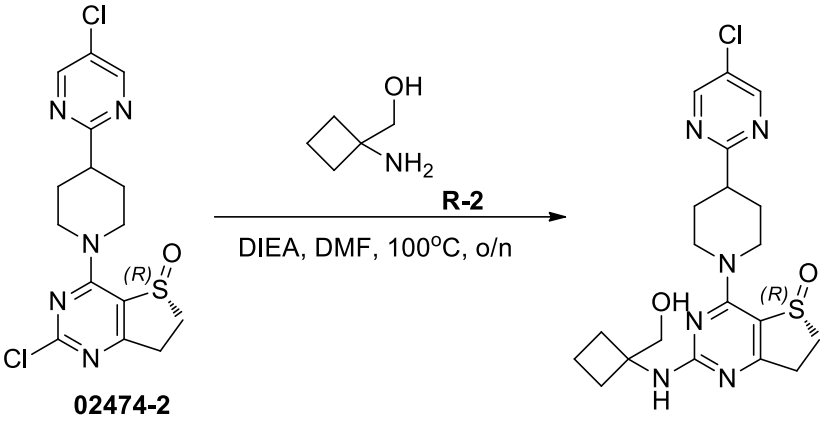
To a solution of 2-chloro-4-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine (45.0 mg, 0.122 mmol) and (S)-1,1'-bi-2-naphthol (3.5 mg, 0.012 mmol) in DCM (5.0 mL) was added titanium tetraisopropoxide (3.5 mg, 0.012 mmol)

and water (4.4 mg, 0.244 mmol). The mixture was stirred at room temperature for 1 hour. 70% tert-butyl hydroperoxide aqueous solution (31.4 mg, 0.244 mmol) was added, and the mixture was stirred at room temperature for 2 hours. Water (10 mL) was added, and the mixture was extracted with DCM (10 mL) three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (DCM/MeOH =1/0 to 10/1, silica gel, 20 g, 30 mL/min, UV 254) to afford the yellow solid (35.0 mg, 74.7% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{15}Cl_2N_5OS]$ $[M+H]^+$: 384.0; found: 384.2

2.3

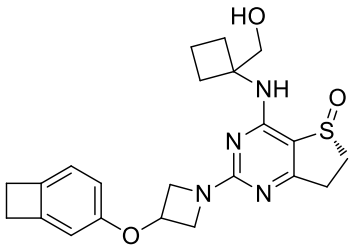
(R)-4-(4-(5-Chloropyrimidin-2-yl)piperidin-1-yl)-2-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02474)



To a solution of (R)-2-chloro-4-(4-(5-chloropyrimidin-2-yl)piperidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (35.0 mg, 0.091 mmol) in DMF (3 mL) was added (1-aminocyclobutyl)methanol (11.0 mg, 0.109 mmol) and DIEA (0.5 mL). The reaction mixture was stirred at 100 °C overnight. The mixture was concentrated in vacuo and the crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (6.0 mg, 14.7% yield).

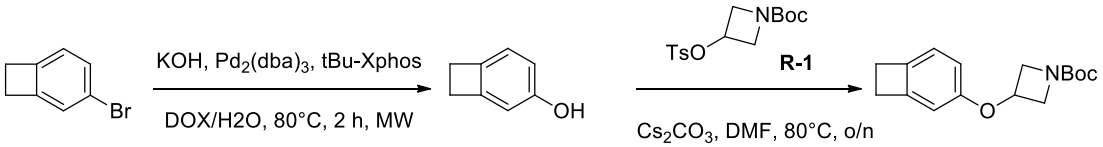
ESI-MS *m/z* calcd for $[C_{20}H_{25}ClN_6O_2S]$ $[M+H]^+$: 449.1; found: 449..3

^{1}H NMR (400 MHz,DMSO-d_6) δ 8.87 (s, 2H), 7.24 (s, 1H), 4.78 – 4.69 (m, 3H), 3.68 – 3.60 (m, 2H), 3.44 – 3.34 (m, 1H), 3.28 – 3.16 (m, 4H), 2.96 – 2.90 (m, 2H), 2.25 – 2.17 (m, 2H), 2.13 – 2.00 (m, 4H), 1.80 –1.68 (m, 4H).

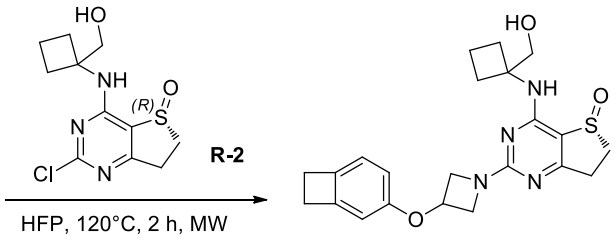


MX02481

1. Synthetic scheme:



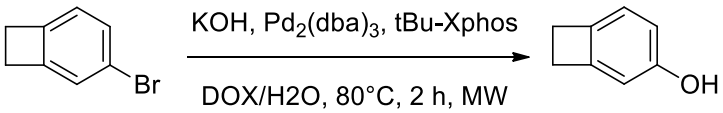
02481-0 **02481-1** **02481-2**



MX02481

2. Experimental section:

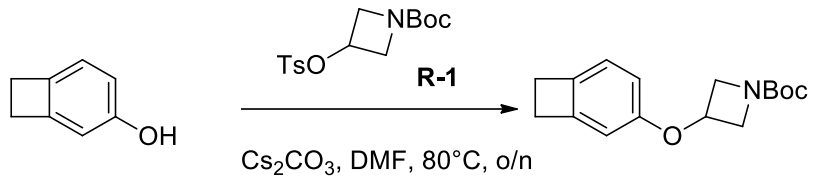
2.1 3-Hydroxybicyclo[4.2.0]oct-1,3,5-triene(02481-1）



02481-0 **02481-1**

To a reaction mixture of 3-bromobicyclo[4.2.0]octa-1,3,5-triene (20 mg, 0.11 mmol), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), tBu-Xphos (5.6 mg, 0.01 mmol), KOH (7.3 mg, 0.1 mmol) and water (0.2 mL) in 1,4-dioxane (2 mL) was stirred under microwave conditions at 80 °C for 2 hours. After the starting material was consumed, the reaction mixture was filtered and concentrated in vacuo for the next step directly.

2.2 tert-Butyl 3-(bicyclo[4.2.0]oct-1,3,5-triene-3-oxy)azetidine-1-carboxylate (02481-2)



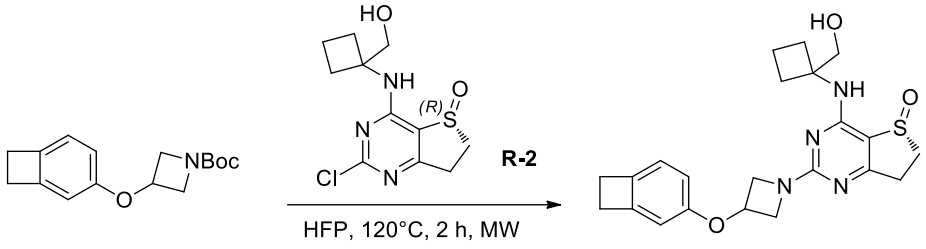
02481-1 **02481-2**

To a solution of 3-hydroxybicyclo[4.2.0]octa-1,3,5-triene (13 mg, 0.11 mmol) and Cs_2CO_3 (107 mg, 0.33 mmol) in DMF (3.0 mL) was added 3-(p-toluenesulfonyloxy)azetidine-1-carboxylic acid tert-butyl ester (49 mg, 0.13 mmol) at room temperature,. The mixture was stirred at 80 °C overnight until the starting material was consumed. Water (10 mL) was added, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE = 0/1 to 1/4, silica gel, 4 g, 25 mL/min, UV 254) to afford the colorless oil (12 mg, 39.7% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{21}NO_3]$ $[M-56+H]^+$: 220.2; found: 220.1

2.3

(R)-2-(3-(bicyclo[4.2.0]oct-1,3, 5-oxo-6,7-dihydrothieno[3,2-d]pyrimidine (MX02481)



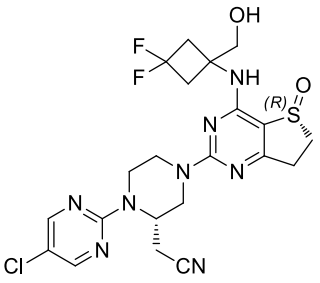
02481-2 **MX02481**

To a solution of 3-((bicyclo[4.2.0]octa-1,3,5-trien-3-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (12 mg, 0.04 mmol) and (R)-2-chloro-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (12 mg, 0.04 mmol) in HFP (2 mL) was stirred under microwave conditions at 120 °C for 2 hours. After the starting material was consumed, water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid compound (1.89 mg, 14.8% yield).

ESI-MS *m/z* calcd for $[C_{22}H_{26}N_4O_3S]$ $[M+H]^+$: 427.2; found: 426.8

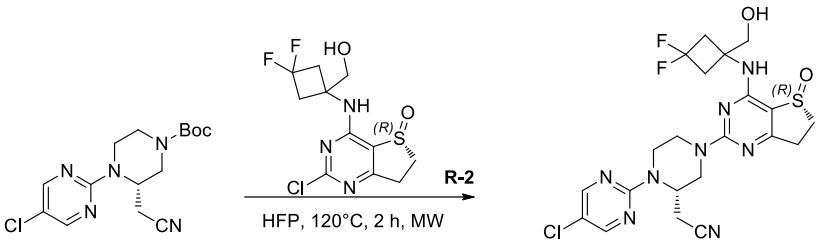
^1H NMR (400 MHz, DMSO-d_6) δ 7.45 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.69 – 6.65 (m,

2H), 5.05 – 5.04 (m, 1H), 4.84 (t, *J* = 5.6 Hz, 1H), 4.44 – 4.41 (m, 2H), 3.89 – 3.88 (m, 2H), 3.73 – 3.69 (m, 2H), 3.45 – 3.36 (m, 1H), 3.25 – 3.17 (m, 1H), 3.07 – 3.06 (m, 4H), 3.00 – 2.84 (m, 2H), 2.38 – 2.25 (m, 2H), 2.15 – 2.10 (m, 2H), 1.82 – 1.68 (m, 2H).



MX02521

1. Synthetic scheme:

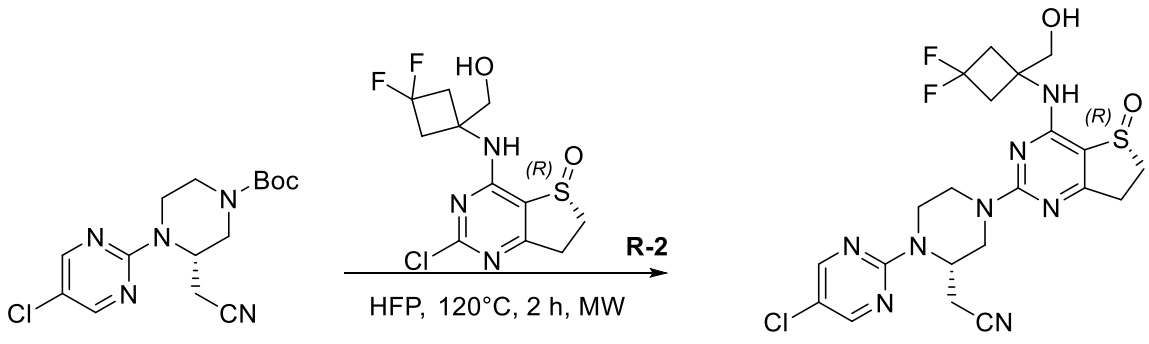


02521-0 **MX02521**

2. Experimental section:

2.1

2-((S)-1-(5-Chloropyrimidin-2-yl)-4-((R)-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)piperazin-2-yl)acetonitrile (MX02521)



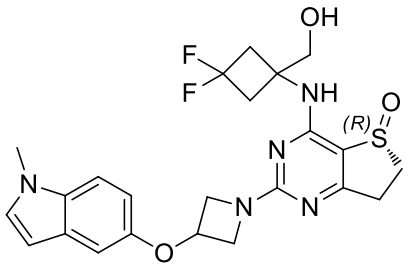
02521-0 **MX02521**

A solution of (S)-tert-butyl 4-(5-chloropyrimidin-2-yl)-3-(cyanomethyl)piperazine-1-carboxylate (10 mg, 0.03 mmol) and (R)-2-chloro-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (10 mg, 0.03 mmol) in HFP (2 mL) was stirred at 120 °C under microwave conditions for 2 hours. Then,

water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (2.80 mg, 17.8% yield).

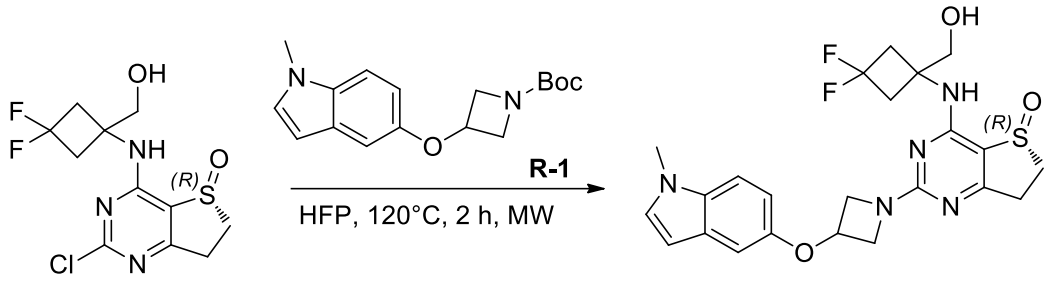
ESI-MS *m/z* calcd for $[C_{21}H_{23}ClF_2N_8O_2S]$ $[M+H]^+$: 525.1; found: 524.6

^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 2H), 8.02 (s, 1H), 5.14 – 5.07 (m, 1H), 4.59 – 4.67 (m, 3H), 3.73 – 3.66 (m, 2H), 3.49 – 3.40 (m, 1H), 3.25 – 3.17 (m, 2H), 3.10 – 3.05 (m, 1H), 3.01 – 2.92 (m, 6H), 2.90 – 2.84 (m, 3H).



MX02532

1. Synthetic scheme:

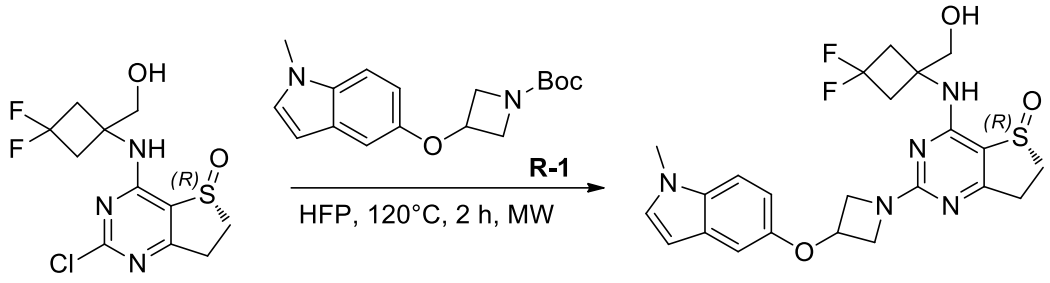


02532-0 **MX02532**

2. Experimental section:

2.1

(R)-4-((3, (R)-4-((3, 3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-2-(3-((1-methyl-1H-indol-5-yl)oxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02532)

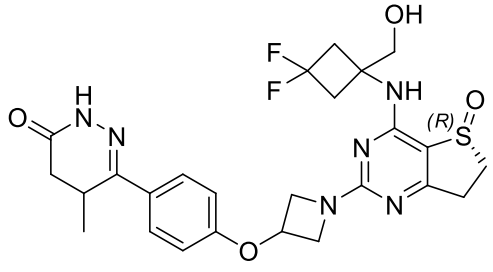


02532-0 **MX02532**

To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)-3,3-difluorocyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (20 mg, 0.062 mmol) and 3-((1-methyl-1H-indol-5-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (20.5 mg, 0.068 mmol) in HFP (3 mL) was stirred under microwave conditions at 120 °C for 2 hours. After the starting material was consumed, water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid compound (15.0 mg, 14.8% yield).

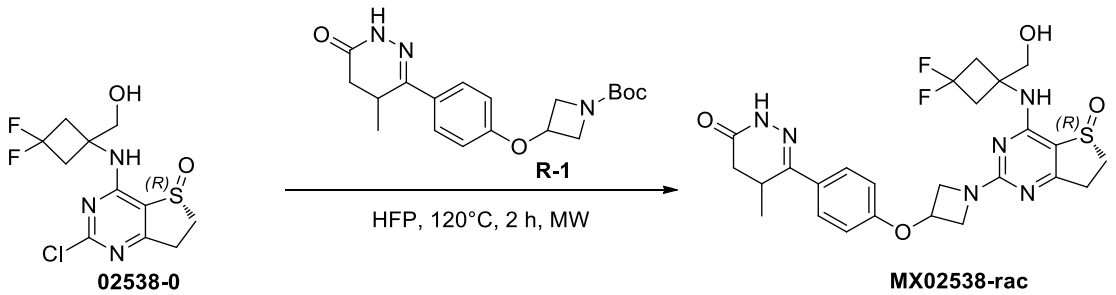
ESI-MS *m/z* calcd for $[C_{23}H_{25}F_2N_5O_3S]$ $[M+H]^+$: 490.2; found: 489.7

^{1}H NMR (400 MHz,DMSO-d_6) δ 7.95 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 3.2 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.78 (dd, J = 8.8, 2.4 Hz, 1H), 6.33 (dd, J = 3.2, 0.8 Hz, 1H), 5.14 – 5.09 (m, 2H), 4.48 – 4.44 (m, 2H), 3.98 – 3.93 (m, 2H), 3.76 (s, 3H), 3.67 – 3.66 (m, 2H), 3.46 – 3.39 (m, 1H), 3.22 –3.17 (m, 1H)，2.99 –2.83 (m, 6H).



MX02538-rac

1. Synthetic scheme:

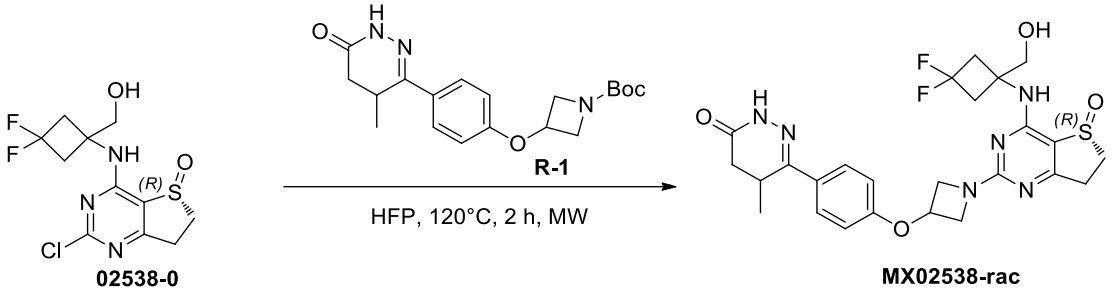


02538-0 **MX02538-rac**

2. Experimental section:

2.1

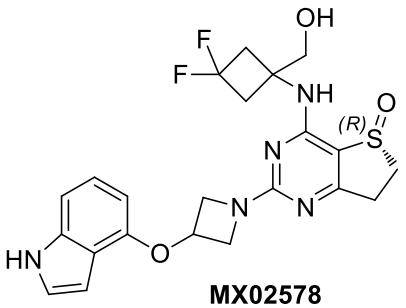
6-(4-((1-((R)-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6, 7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)phenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one(MX02538-rac)



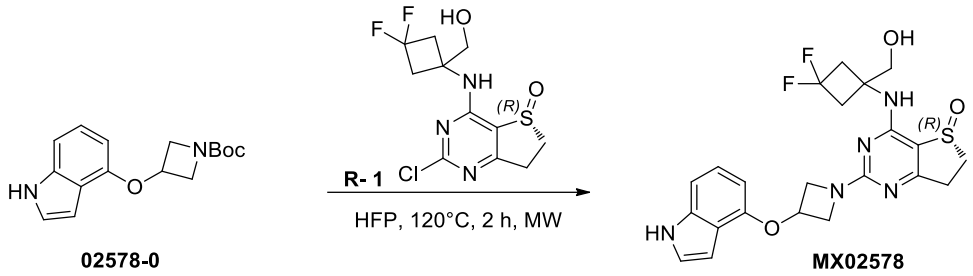
To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)-3,3-difluorocyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (20 mg, 0.062 mmol) and 3-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy)azetidine-1-carboxylic acid tert-butyl ester (22 mg, 0.062 mmol) in HFP (2 mL) was stirred under microwave conditions at 120 °C for 2 hours. After the reaction was completed, the mixture was concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid (5.37 mg, 15.9% yield).

ESI-MS *m/z* calcd for [$C_{25}H_{28}F_2N_6O_4S$] $[M+H]^+$:547.2; found:547.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.99 (s, 1H),7.76 (d, *J* = 9.2 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.18 – 5.12 (m, 2H), 4.49 (dd, *J* = 9.6, 6.0 Hz, 2H)，3.95 (br, 2H), 3.71 – 3.63 (m, 2H), 3.46 – 3.36 (m, 2H), 3.23 – 3.17 (m, 1H), 3.00 – 2.83 (m, 6H), 2.70 – 2.64 (m, 1H), 2.23 (d, *J* = 16.4 Hz, 1H), 1.07 (t, *J* = 7.2 Hz, 3H).



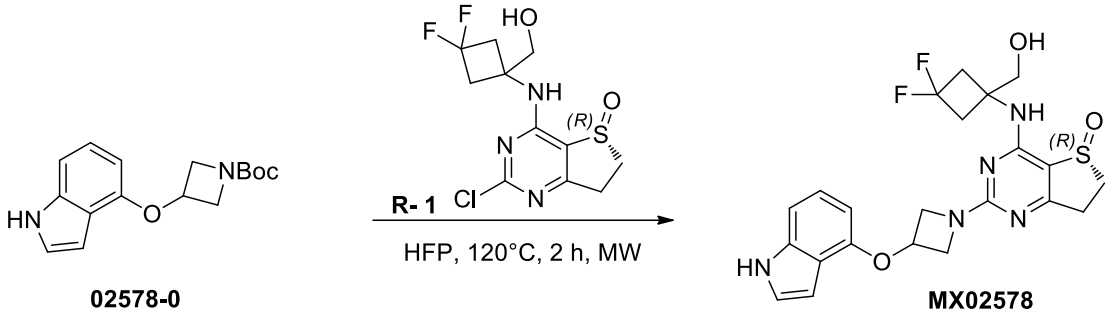
1. Synthetic scheme:



2. Experimental section:

2.1

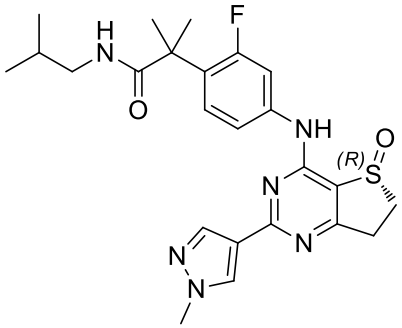
(R)-2-(3-((1H-indol-4-yl)oxy)azetidin-1-yl)-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide(MX02578)



To a solution of 3-((1H-indol-4-yl)oxy)azetidine-1-carboxylic acid tert-butyl ester (9.7 mg, 0.03 mmol) and (R)-2-chloro-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidin-5-oxide (10 mg, 0.03 mmol) in HFP (2 mL) was stirred under microwave conditions at 120 °C for 2 hours. After the starting material was consumed, water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid compound (4.91 mg, 34.4% yield).

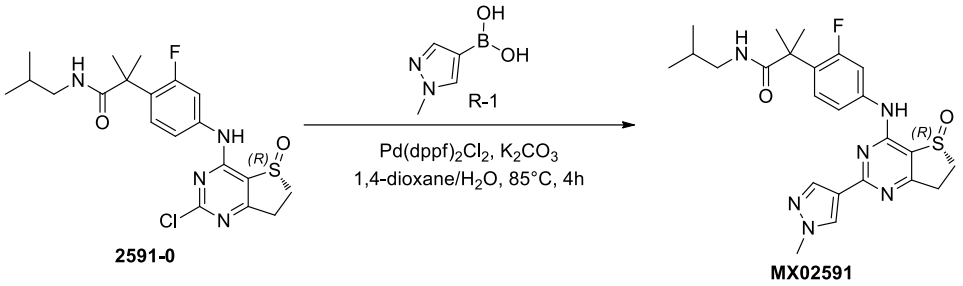
ESI-MS *m/z* calcd for $[C_{22}H_{23}F_2N_5O_3S]$ $[M+H]^+$: 476.2; found: 476.1

^{1}H NMR (400 MHz, DMSO-d_6) δ11.14 (s, 1H),7.97 (s, 1H), 7.25 (t, J = 2.8 Hz, 1H), 7.06 – 7.04 (m, 1H), 6.99 (t, J = 8.0 Hz, 1H), 6.49 – 4.42 (m, 1H), 6.30 (d, J = 7.6 Hz, 1H), 5.23 – 5.19 (m, 1H), 5.13 (t, J = 5.6 Hz, 1H), 4.55 – 4.50 (m, 2H), 4.01 – 3.97 (m, 2H), 3.68 – 3.63 (m, 2H), 3.48 – 3.40 (m, 1H), 3.24 – 3.17 (m, 1H), 3.00 – 2.81 (m, 6H).



MX02591

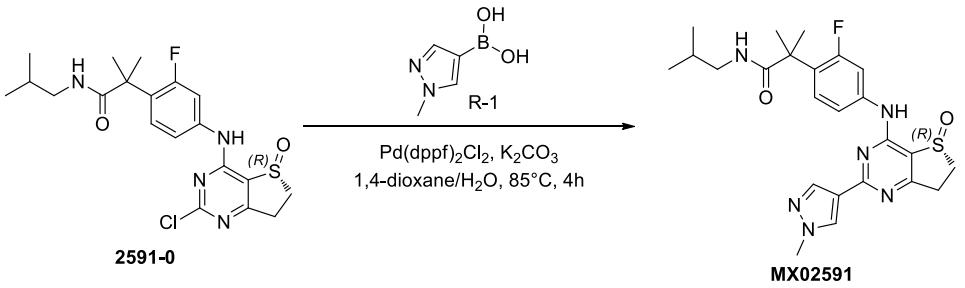
1. Synthetic scheme:



2. Experimental section:

2.1

(R)-2-(2-Fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl) -N-isobutyl-2-methylpropanamide(MX02591)

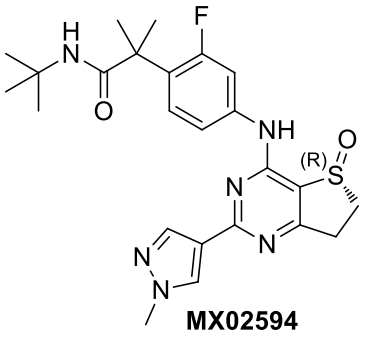


To a solution of (R)-2-(4-((2-chloro-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-N-isobutyl-2-methylpropanamide (30 mg, 0.07 mmol) in 1,4-dioxane/water (5 mL, v/v = 4:1) was added 1-methyl-1H-pyrazol-4-ylboronic acid (17 mg, 0.14 mmol), K_2CO_3 (28 mg, 0.20 mmol), and $Pd(dppf)Cl_2$ (7 mg, 0.01 mmol). The mixture was stirred under a nitrogen atmosphere at 85 °C for 4 hours. After the reaction was completed, the mixture was concentrated in vacuo. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the pale yellow solid (4.41 mg, 13.32% yield).

ESI-MS *m/z* calcd for $[C_{24}H_{29}FN_6O_2S]$ $[M+H]^+$:485.2; found:484.6

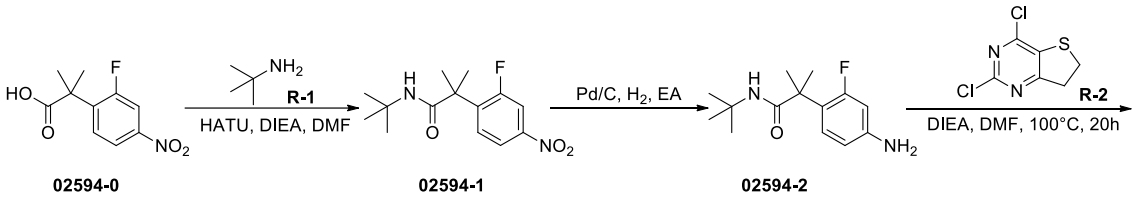
^1H NMR (400 MHz, DMSO-d_6) δ 8.24 (s,1H), 8.08 (s, 1H), 7.66 – 7.58 (m, 2H), 7.49 (t,

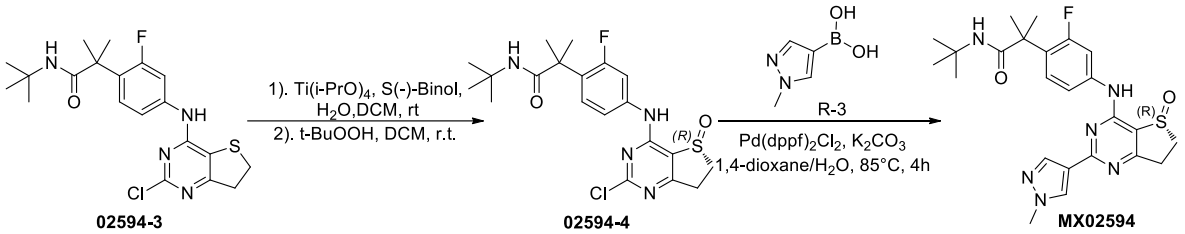
J = 8.8Hz, 1H), 7.30 (t, *J* = 5.6 Hz, 1H), 3.97 (s, 3H), 3.85 – 3.76 (m, 1H), 3.55 – 3.48 (m, 1H), 3.39 – 3.35 (m, 1H), 3.26 – 3.12 (m, 1H), 2.98 (t, *J* = 6.4Hz, 2H), 1.84 – 1.77 (m, 1H), 1.57 (s, 6H), 0.87 (s, 3H), 0.86 (s,3H).



MX02594

1. Synthetic scheme:

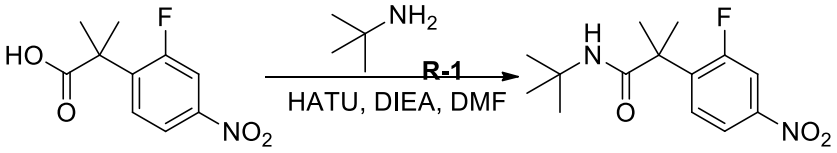




2. Experimental section:

2.1

N-(tert-butyl)-2-(2-fluoro-4-nitrophenyl)-2-methylpropanamide(02594-1)



02594-0 **02594-1**

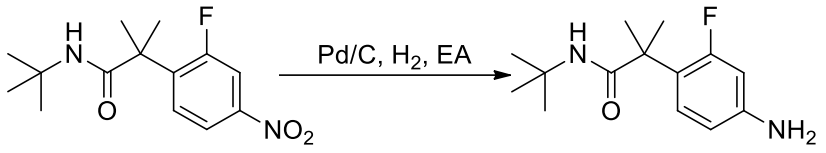
To a solution of 2-(2-fluoro-4-nitrophenyl)-2-methylpropanoic acid (1.0 g, 4.40 mmol) in DMF (20 mL) was added tert-butylamine (0.97 g, 13.20 mmol), HATU (3.35 g, 8.80 mmol), and DIEA (1.71 g, 13.20 mmol). The mixture was stirred at room temperature for 16 hours. The mixture was poured into water (50 mL) and extracted with EA (50 mL) twice. The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column

chromatography (EA/PE=0 to 50%, silica gel, 40 g, 50 mL/min, UV 254) to afford the colorless oil (1.1 g, 88.52% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{19}FN_2O_3]$ $[M+H]^+$:283.1; found:283.4

2.2

2-(4-Amino-2-fluorophenyl)-N-(tert-butyl)-2-methylpropanamide(02594-2)



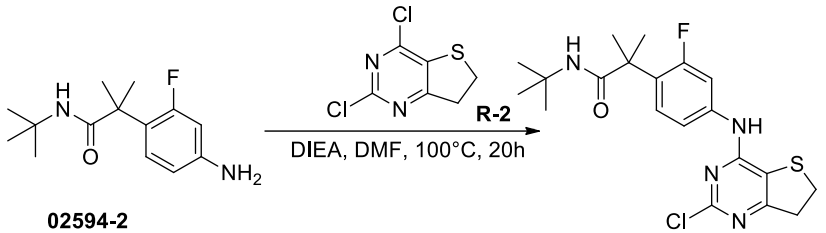
02594-1 **02594-2**

To a solution of N-(tert-butyl)-2-(2-fluoro-4-nitrophenyl)-2-methylpropanamide (1.1 g, 3.90 mmol) in EA (40 mL) was added Pd/C (0.2 g). The mixture was stirred at room temperature under a hydrogen atmosphere for 16 hours. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (EA/PE 0 to 70%, silica gel, 40 g, 50 mL/min, UV 254) to afford the colorless oil (0.9 g, 91.54% yield).

ESI-MS m/z calcd for $[C_{14}H_{21}FN_2O]$ $[M+H]^+$:253.2; found:253.2

2.3

N-(tert-butyl)-2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-2-methylpropanamide(02594-3)



02594-2 **02594-3**

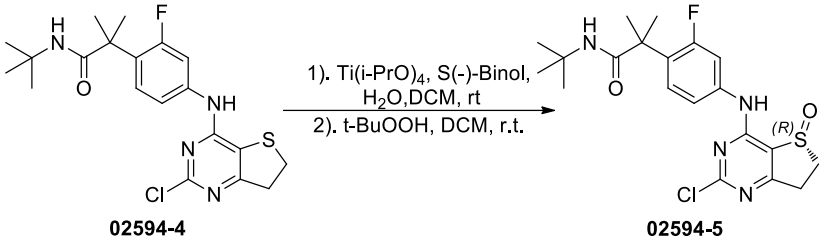
To a solution of 2-(4-amino-2-fluorophenyl)-N-(tert-butyl)-2-methylpropanamide (500 mg, 1.98 mmol) and 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidine (1.23 g, 5.95 mmol) in DMF (20 mL) was added DIEA (1.02 g, 7.93 mmol). The mixture was stirred at 100 °C for 20 hours. After the reaction was completed, the mixture was concentrated in vacuo. The crude product was purified by column chromatography (EA/PE= 0 to 75%, silica gel, 20 g, 25 mL/min, UV 254) to afford the yellow solid (185 mg, 22.07% yield).

ESI-MS m/z calcd for $[C_{20}H_{24}ClFN_4OS]$ $[M+H]^+$:423.1; found:423.1

2.4

(R)-N-(tert-butyl)-2-(4-((2-chloro-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-

yl)amino)-2-fluorophenyl)-2-methylpropanamide(02594-5)



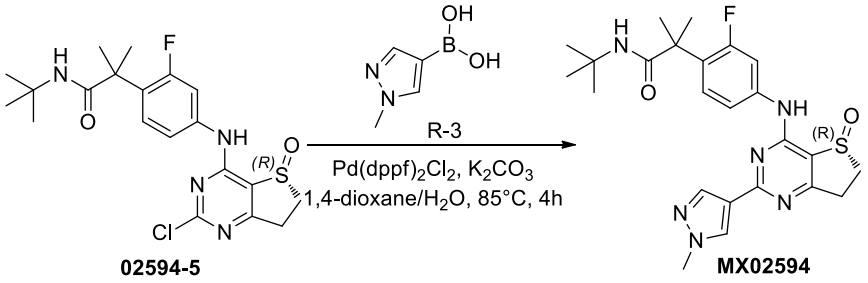
02594-4 02594-5

To a solution of N-(tert-butyl)-2-(4-((2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-2-methylpropanamide (185 mg, 0.44 mmol) and (S)-1,1'-bi-2-naphthol (25 mg, 0.09 mmol) in DCM (10 mL) was added titanium tetraisopropoxide (25 mg, 0.09 mmol) and water (16 mg, 0.88 mmol). The mixture was stirred at room temperature for 16 hours. 70% tert-butyl hydroperoxide aqueous solution (169 mg, 1.31 mmol) was added in one portion, and the mixture was stirred at room temperature for 2 hours. Water (10 mL) was added, and the mixture was extracted with DCM (30 mL) three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (MeOH/DCM = 0 to 5%, silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid (106 mg, 55.21% yield).

ESI-MS *m/z* calcd for $[C_{20}H_{24}ClFN_4O_2S]$ $[M+H]^+$:439.1; found:439.0

2.5

(R)-N-(tert-butyl)-2-(2-fluoro-4-((2-(1-methyl-1H-pyrazol-4-yl)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)phenyl) -2-methylpropanamide (MX02594)



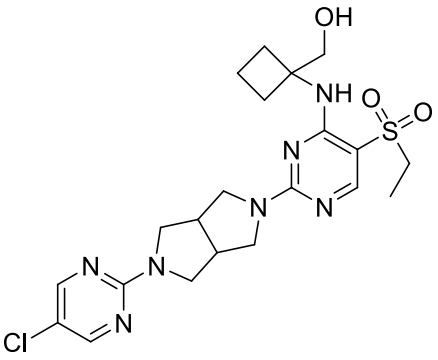
02594-5 MX02594

To a solution of (R)-N-(tert-butyl)-2-(4-((2-chloro-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-2-methylpropanamide (35 mg, 0.08 mmol) in 1,4-dioxane/water (5 mL, v/v = 4:1) was added 1-methyl-1H-pyrazol-4-ylboronic acid (20 mg, 0.16 mmol), K_2CO_3 (33 mg, 0.24 mmol), and $Pd(dppf)Cl_2$ (7 mg, 0.01 mmol). The mixture was stirred under a nitrogen atmosphere at 85 °C for 4 hours. After the reaction was completed, the mixture was concentrated in vacuo. The crude product was purified by preparative HPLC

[MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select10 μm 19*250 mm, 20 mL/min, UV 254] to afford the pale yellow solid (7.67 mg, 19.85% yield).

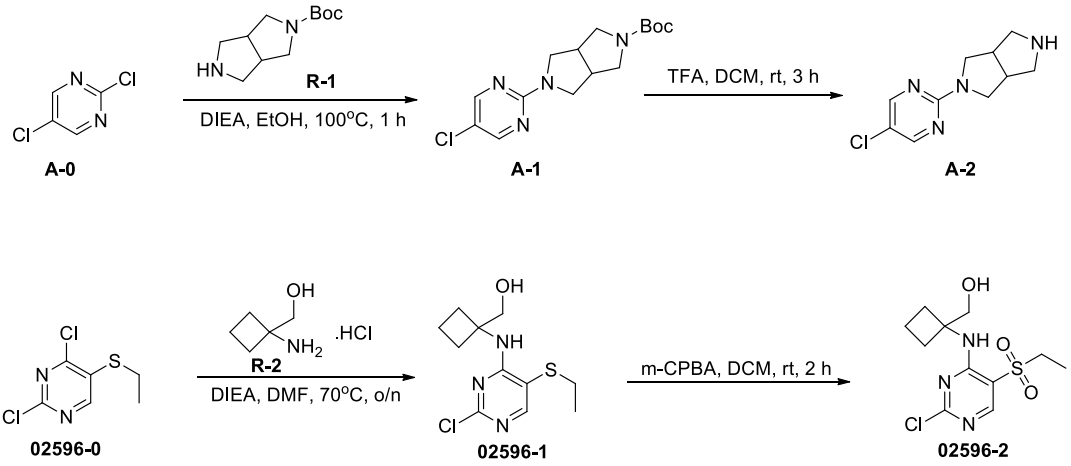
ESI-MS *m/z* calcd for [$C_{24}H_{29}FN_6O_2S$] $[M+H]^+$:485.2; found:484.6

^1H NMR (400 MHz, DMSO-d_6) δ8.27 (s,1H), 8.11 (s, 1H), 7.67 – 7.61 (m, 2H), 7.51 (t, *J* = 9.2Hz, 1H), 6.13 (s, 1H), 3.99 (s, 3H), 3.85 – 3.80 (m, 1H), 3.55 – 3.49 (m, 1H), 3.42 – 3.35 (m, 1H), 3.28 – 3.21 (m, 1H), 1.56 (s, 6H), 1.33 (s, 9H).



MX02596

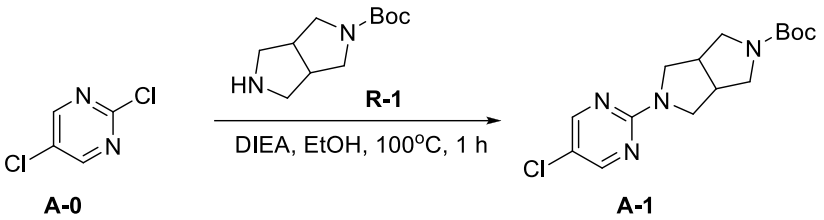
1. Synthetic scheme:



2. Experimental section:

2.1

5-(5-Chloropyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylic acid tert-butyl ester(A-1)

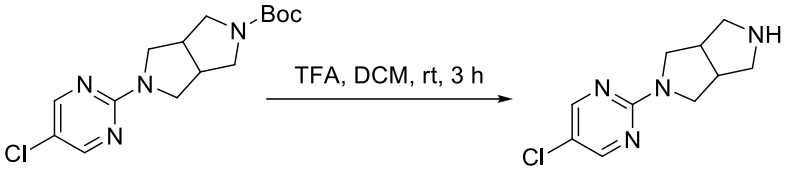


A-0 A-1

To a solution of tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (72 mg, 0.36 mmol) in EtOH (2 mL) was added 2,5-dichloropyrimidine (50 mg, 0.36 mmol) and DIEA (139 mg, 1.08 mmol). The mixture was stirred at 100 °C under a nitrogen atmosphere for 1 hour. After the starting material was consumed, water (30 mL) was added to the mixture, and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE= 0/1 to 1/1, silica gel, 12 g, 30 mL/min, UV 254) to afford the white solid (86 mg, 74% yield).

ESI-MS *m/z* calcd for $[C_{15}H_{21}ClN_4O_2]$ $[M-56+H]^+$: 269.1; found: 269.1

2.2 2-(5-Chloropyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole(A-2)



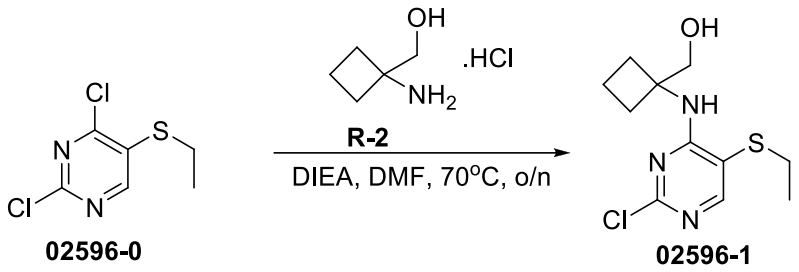
A-1 A-2

To a solution of 5-(5-chloropyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylic acid tert-butyl ester (30 mg, 0.09 mmol) in DCM (2 mL) was added TFA (0.2 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 3 hours. After the starting material was consumed, the mixture was concentrated in vacuo to afford the white solid (19 mg, 92% yield), which was used directly for the next step.

ESI-MS *m/z* calcd for $[C_{10}H_{13}ClN_4]$ $[M+H]^+$: 225.1; found: 225.1

2.3

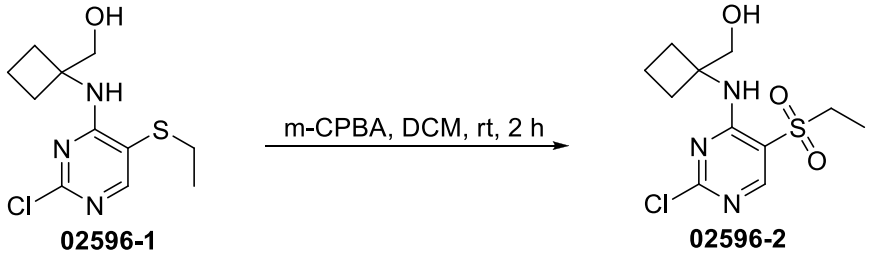
(1-(2-Chloro-5-(ethylthio)pyrimidin-4-ylamino)cyclobutyl)methanol (02596-1)



To a solution of 2,4-dichloro-5-(ethylthio)pyrimidine (100 mg, 0.48 mmol) in DMF (4 mL) was added (1-aminocyclobutyl)methanol hydrochloride (48.6 mg, 0.48 mmol) and DIEA (185.8 mg, 1.44 mmol). The mixture was stirred at 70 °C overnight until the starting material was consumed. Water (30 mL) was added, and the mixture was extracted with EA (50 mL) three times. The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EA/PE 0/1 to 1/1, silica gel, 20 g, 30 mL/min, UV 254) to afford the white solid (81 mg, 62% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{16}ClN_3OS]$ $[M+H]^+$: 274.1; found: 274.0

2.4 (1-(2-Chloro-5-(ethylsulfonyl)pyrimidin-4-ylamino)cyclobutyl)methanol (02596-2)



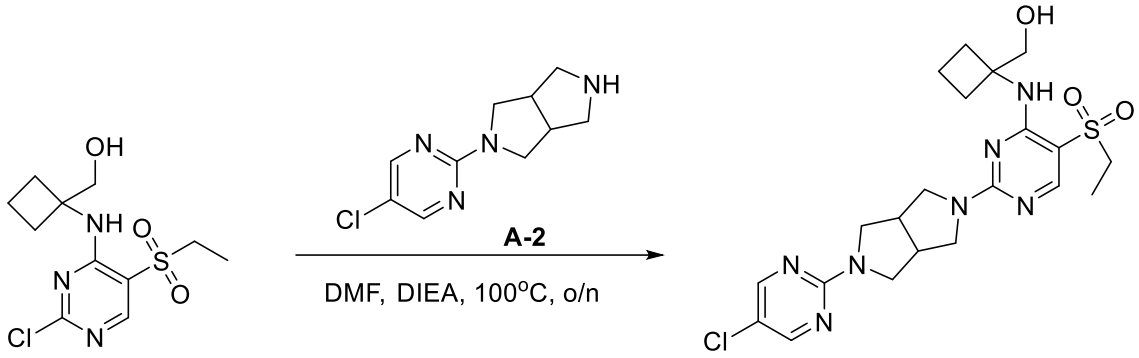
To a solution of (1-((2-chloro-5-(ethylthio)pyrimidin-4-yl)amino)cyclobutyl)methanol (70 mg, 0.26 mmol) in DCM (10 mL) was added m-CPBA (85%, 154.7 mg, 0.76 mmol). The mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours. Upon completion of the consumption of the starting material, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with EA (30 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0:1 to 1:2, Silica gel 20 g, 20 mL/min, Silica gel, UV 254) to afford the white solid product (64 mg, 79% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{16}ClN_3O_3S]$ $[M+H]^+$: 306.1; found: 306.0

2.5

(1-((2-(5-(5-Chloropyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-

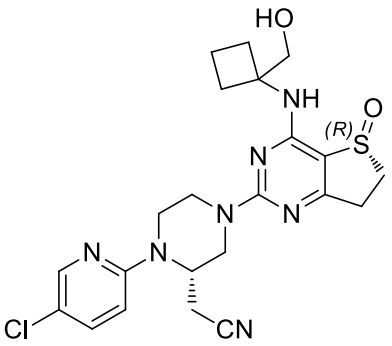
(ethylsulfonyl)pyrimidin-4-yl)amino)cyclobutyl)methanol (MX02596)



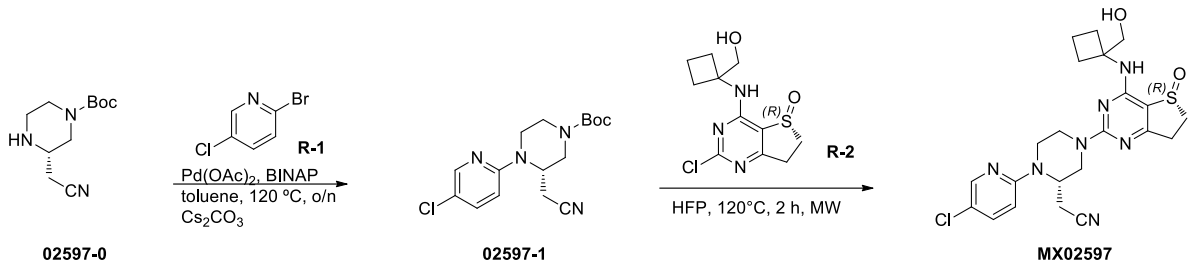
To a solution of (1-(2-chloro-5-(ethylsulfonyl)pyrimidin-4-ylamino)cyclobutyl)methanol (26 mg, 0.085 mmol) and 2-(5-chloropyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole (19 mg, 0.085 mmol) in DMF (2 mL) was added DIEA (33 mg, 0.255 mmol) The mixture was stirred overnight at 100°C under a nitrogen atmosphere. After the consumption of the starting material, the mixture was concentrated under reduced pressure to remove the solvent. The obtained crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254] to afford the white solid product (21.36 mg, 51% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{28}ClN_7O_3S]$ $[M+H]^+$:494.2; found:493.7

^1H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 2H), 8.13 (s, 1H), 6.93 (s, 1H), 4.89 (t, *J* = 5.6 Hz, 1H)，3.84 – 3.70 (m, 6H), 3.49 – 3.38 (m, 4H), 3.17 (q, *J* = 7.6 Hz, 2H), 3.10 (br, 2H), 2.34 – 2.29 (m, 2H), 2.13 – 2.08 (m, 2H), 1.85 – 1.74 (m, 2H), 1.13 (t, *J* = 7.2 Hz, 3H).



1. Synthetic scheme:

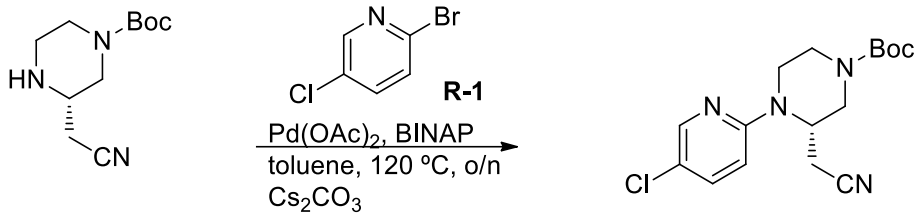


02597-0 02597-1 MX02597

2. Experimental section:

2.1

(S)-4-(5-Chloropyridin-2-yl)-3-(cyanomethyl)piperazine-1-carboxylic acid tert-butyl ester (02597-1)



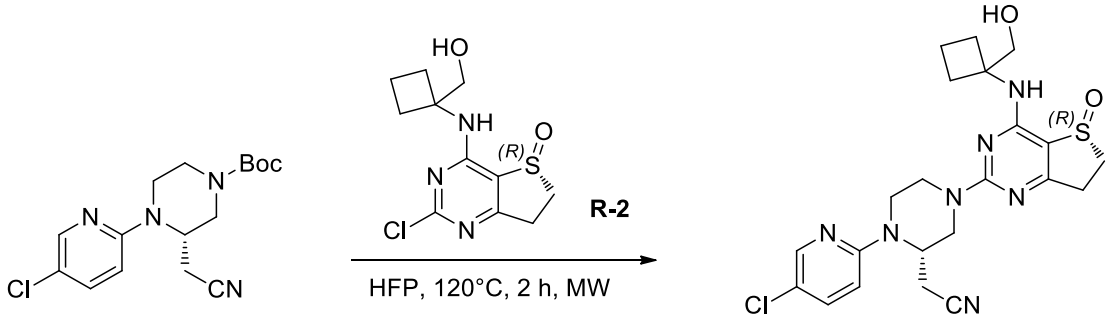
02597-0 **02597-1**

A mixture of tert-butyl 3-(cyanomethyl)piperazine-1-carboxylate (100 mg, 0.44 mmol), 2-bromo-5-chloropyridine (86 mg, 0.45 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), BINAP (40 mg, 0.06 mmol) and Cs_2CO_3 (390 mg, 1.2 mmol) in toluene (8 mL) was stirred overnight at 120 °C under an argon atmosphere. After cooling, the reaction mixture was concentrated under reduced pressure to remove the solvent. The crude product was purified by column chromatography (EA/PE = 0/1~1/9, Silica gel-CS 20 g, 36 mL/min, Silica, UV 254) to afford the colorless oil product (103 mg, 69.6% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{21}ClN_4O_2]$ $[M-56+H]^+$: 281.1; found: 281.1

2.2

2-((S)-1-(5-chloropyridin-2-yl)-4-((R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl) piperazin-2-yl)acetonitrile (MX02597)

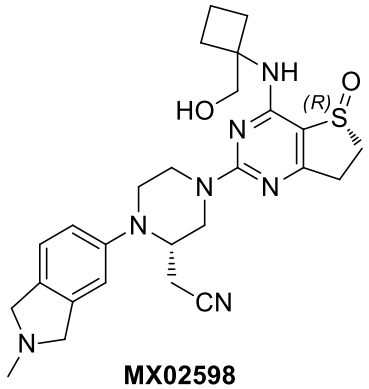


02597-1 **MX02597**

A solution of (S)-tert-butyl 4-(5-chloropyridin-2-yl)-3-(cyanomethyl)piperazine-1-carboxylate (20 mg, 0.09 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (30 mg, 0.11 mmol) in HFP (2 mL) was stirred for 2 hours at 120 °C under microwave irradiation. Then, water (10 mL) was added to the mixture, and it was extracted twice with DCM (10 mL). The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid compound (7.97 mg, 18.1% yield).

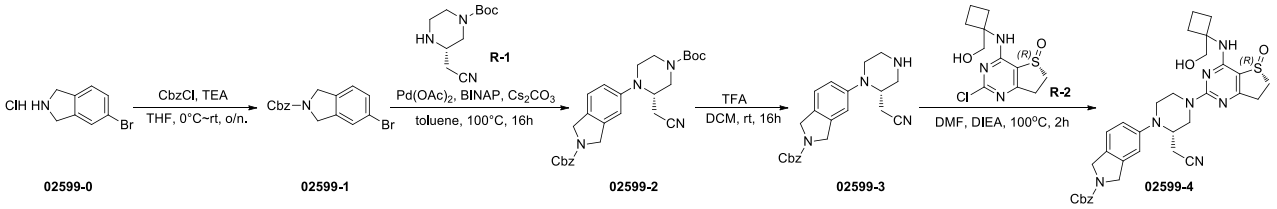
ESI-MS *m/z* calcd for $[C_{22}H_{26}ClN_7O_2S]$ $[M+H]^+$: 488.2; found: 487.6

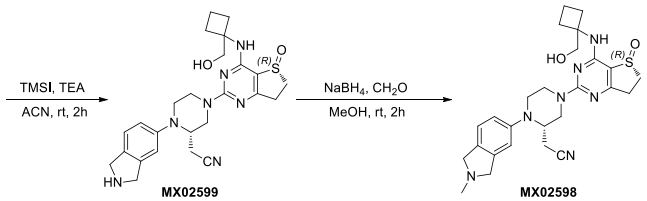
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, *J* = 2.8 Hz, 1H), 7.68 (dd, *J* = 11.2, 2.4 Hz, 1H), 7.44 (s, 1H), 6.96 (d, *J* = 9.6 Hz, 1H), 4.95 – 4.94 (m, 1H), 4.81 (t, *J* = 5.2 Hz, 1H), 4.64 – 4.61 (m, 1H), 4.52 – 4.50 (m, 1H), 4.07 – 4.04 (m, 1H), 3.76 – 3.69 (m, 2H), 3.46 – 3.35 (m, 2H), 3.36 – 3.10 (m, 3H), 2.99 – 2.85 (m, 2H), 2.79 – 2.67 (m, 2H), 2.43 – 2.27 (m, 2H), 2.22 – 2.17 (m, 2H), 1.85 – 1.71 (m, 2H).



MX02598

1. Synthetic scheme:

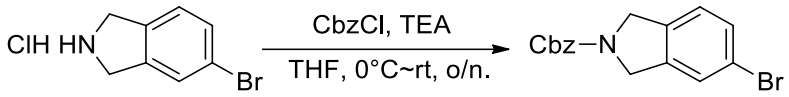




2. Experimental section:

2.1

5-Bromoisoindolin-2-carboxylic acid benzyl ester(02599-1)



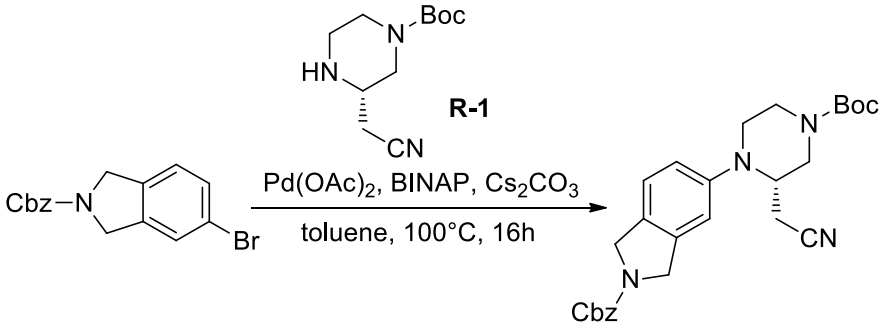
02599-0 **02599-1**

To a solution of 5-bromoisoindoline hydrochloride (393 mg, 1.68 mmol) in THF (6 mL) TEA (592 mg, 5.86 mmol) and benzyl chloroformate (429 mg, 2.51 mmol) were added at 0 °C. The mixture was stirred overnight at room temperature. Water (50 mL) was added, and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product. The crude product was purified by silica gel column chromatography (EA/PE = 0/1 to 1/5, Silica gel-CS 40 g, 40 mL/min, Silica, UV 254) to give the brown solid (499 mg, 90% yield).

ESI-MS *m/z* calcd for $[C_{16}H_{14}BrNO_2]$ $[M+Na]^+$: 354.0; found: 354.1

2.2

(S)-5-(4-(Tert-butoxycarbonyl)-2-(cyanomethyl)piperazin-1-yl)isoindolin-2-carboxylic acid benzyl ester(02599-2)



02599-1 **02599-2**

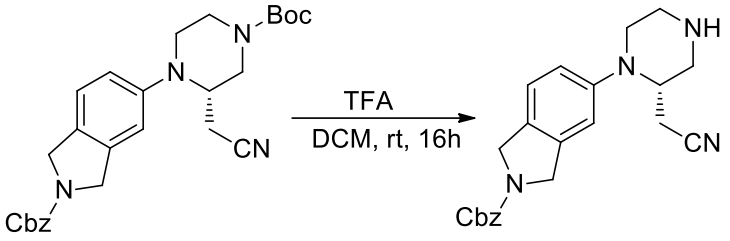
To a solution of benzyl 5-bromoisoindoline-2-carboxylate (242 mg, 1.07 mmol) and (S)-tert-butyl 3-(cyanomethyl)piperazine-1-carboxylate (392 mg, 1.18 mmol) in toluene (10 mL) at room temperature under a nitrogen atmosphere, BINAP (67 mg, 0.11 mmol), $Pd(OAc)_2$ (24 mg, 0.11 mmol), and Cs_2CO_3 (1.05 g, 3.22 mmol) were added. The reaction mixture was then stirred at 100 °C for 16 hours. After the reaction was completed, water (50 mL) was added to quench the reaction, and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous

Na_2SO_4, filtered and concentrated to afford the crude product. The crude product was purified by silica gel column chromatography (EA/PE = 0/1 to 1/1, Silica gel 40 g, 40 mL/min, Silica, UV 254) to afford the yellow oil product (188 mg, 37% yield).

ESI-MS *m/z* calcd for $[C_{27}H_{32}N_4O_4]$ $[M+H]^+$: 477.2; found: 477.3

2.3

(S)-5-(2-(Cyanomethyl)piperazin-1-yl)isoindolin-2-carboxylic acid benzyl ester(02599-3)



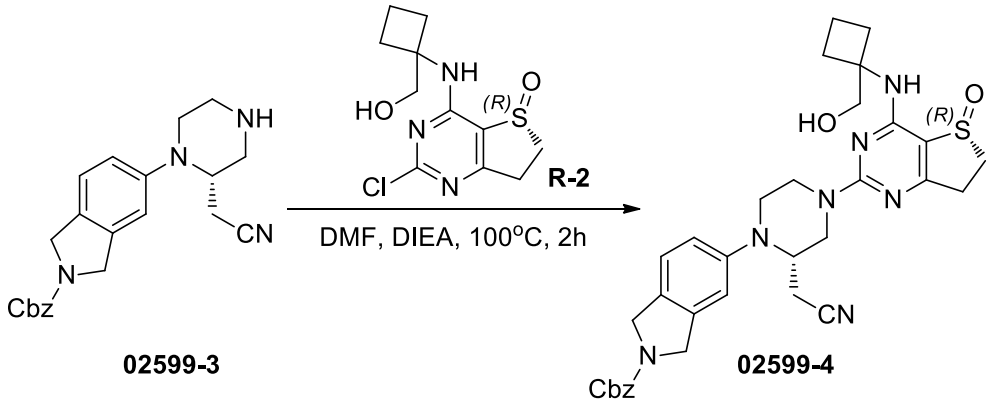
02599-2 **02599-3**

To a solution of benzyl (S)-5-((S)-4-(tert-butoxycarbonyl)-2-(cyanomethyl)piperazin-1-yl)isoindoline-2-carboxylate (188 mg, 0.39 mmol) in DCM (6 mL) was added TFA (1 mL) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 16 hours. Upon completion of the reaction, the reaction mixture was evaporated to dryness under reduced pressure to afford the crude product. The crude product was purified by preparative reversed-phase HPLC [MeCN/H2O (0.5% HCOOH), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254] to afford the target product (99 mg, 67% yield).

ESI-MS *m/z* calcd for $[C_{22}H_{24}N_4O_2]$ $[M+H]^+$: 377.2; found: 377.2.

2.4

5-((S)-2-(Cyanomethyl)-4-((R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl) piperazin-1-yl)isoindolin-2-carboxylic acid benzyl ester(02599-4)



02599-3 **02599-4**

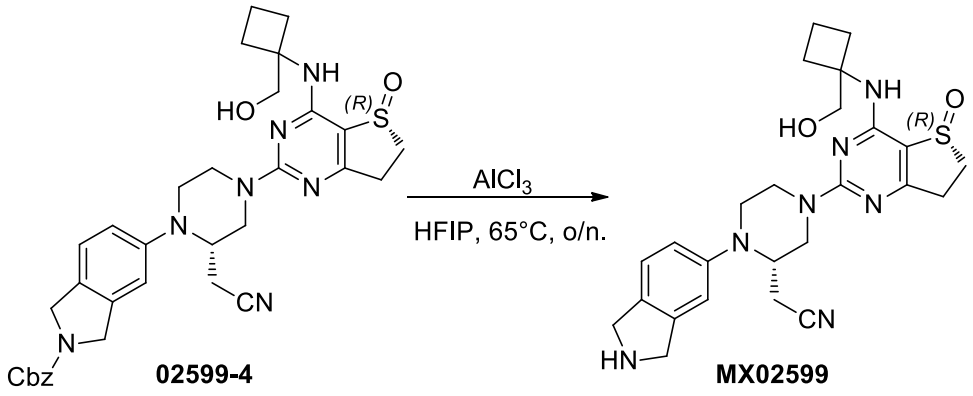
To a solution of benzyl (S)-5-((2-(cyanomethyl)piperazin-1-yl)isoindoline-2-carboxylate

(113 mg, 0.30 mmol) in DMF (5 mL) were added (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (86 mg, 0.30 mmol) and DIEA (194 mg, 1.50 mmol). The mixture was stirred at 100°C under nitrogen for 2 hours. After the reaction was completed, water (30 mL) was added, and the mixture was extracted with EA (10 mL × 3). The combined organic layers were washed with saturated saturated brine, dried over Na_2SO_4, filtered and concentrated to afford the crude product. The crude product was purified by preparative reversed-phase HPLC [MeCN/H_2O (0.5% HCOOH), X-Select 10 μm, 19×250 mm, 20 mL/min, UV 254] to afford the target product (120 mg, 67% yield).

ESI-MS *m/z* calcd for $[C_{33}H_{37}N_7O_4S]$ $[M+H]^+$: 628.3; found: 628.2.

2.5

2-((S) 2-(((S)-4-((R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)-1-(isoindolin-5-yl)piperazin-2-yl)acetonitrile(MX02599)

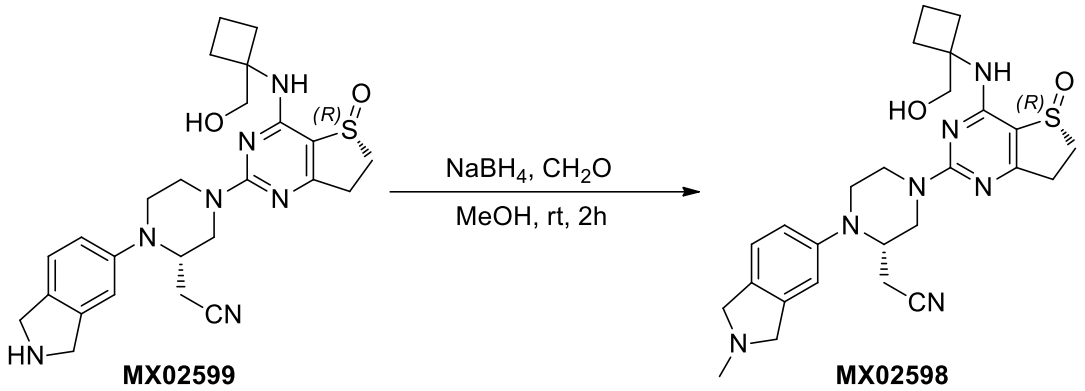


To a solution of benzyl (S)-5-((2-(cyanomethyl)-4-((R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)piperazin-1-yl)isoindoline-2-carboxylate (70 mg, 0.11 mmol) in HFP (6 mL) was added $AlCl_3$ (74 mg, 0.55 mmol) at 0°C under a nitrogen atmosphere. The mixture was stirred at 65°C overnight. The mixture was filtered through diatomaceous earth and concentrated in vacuo to afford the crude product. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19×250 mm, 20 mL/min, UV 254] to afford the white solid product (49 mg, 89% yield).

ESI-MS *m/z* calcd for $[C_{25}H_{31}N_7O_2S]$ $[M+H]^+$: 494.2; found: 494.2.

2.6

2-((S)-4-((R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxy-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)-1-(2-methylisindolin-5-yl)piperazin-2-yl)acetonitrile(MX02598)

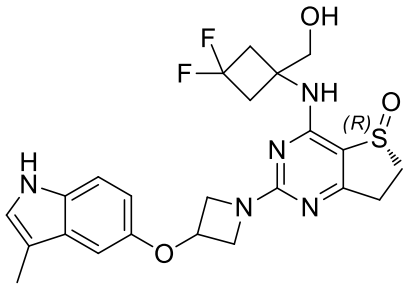


MX02599 MX02598

To a solution of 2-((S)-4-((R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)-1-(isoindolin-5-yl)piperazin-2-yl)acetonitrile (30 mg, 0.06 mmol) in MeOH (3 mL) under nitrogen at room temperature were added 35% formaldehyde aqueous solution (0.5 mL) and sodium borohydride (5 mg, 0.13 mmol). The mixture was stirred at room temperature for 2 h. Upon completion, the pH of the reaction mixture was adjusted to 6-7 with dilute HCl (0.5 N), and the mixture was concentrated to afford the crude product. The crude product was purified by preparative HPLC [MeCN/H_2O (0.5% HCOOH), X-Select 10 μm 19×250 mm, 20 mL/min, UV 254] to afford the white solid product (3.45 mg, 10% yield).

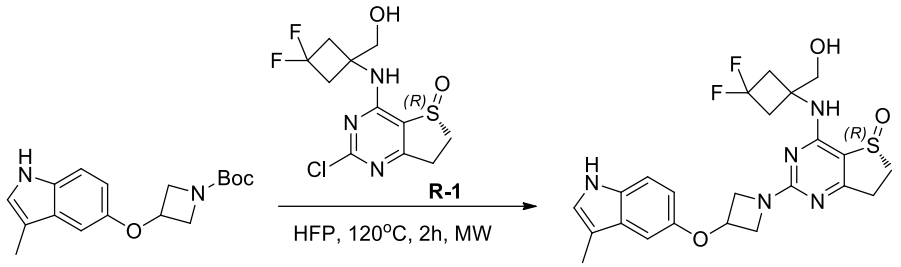
ESI-MS *m/z* calcd for $[C_{26}H_{33}N_7O_2S]$ $[M+H]^+$: 508.2; found: 508.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.10 （d, J = 8.0 Hz, 1H）， 6.91 (s, 1H), 6.85 (dd, J = 8.4, 2.0 Hz, 1H), 4.82– 4.81 (m, 1H), 4.45 – 4.38 (m, 2H), 4.25 – 4.22 (m, 1H), 3.77 – 3.70 (m, 6H), 3.53 (dd, J = 13.2, 3.2Hz, 1H), 3.30 – 3.20 (m, 4H), 3.07 – 2.86 (m, 3H), 2.67 – 2.60 (m, 1H), 2.46 (s, 3H), 2.43 – 2.27 (m, 3H), 2.22 – 2.17 (m, 2H), 1.83 – 1.71 (m, 2H).



MX02605

1. Synthetic scheme:

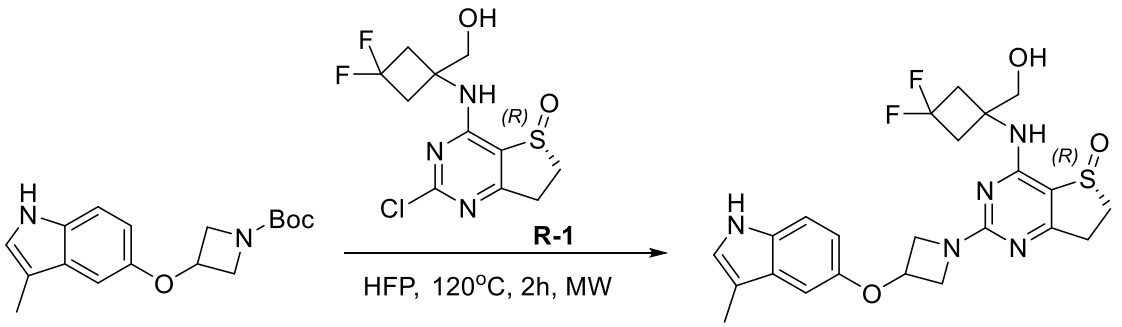


02605-0 MX02605

2. Experimental section:

2.1

(R)-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-2-(3-((3-methyl-1H-indol-5-yl)oxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02605)

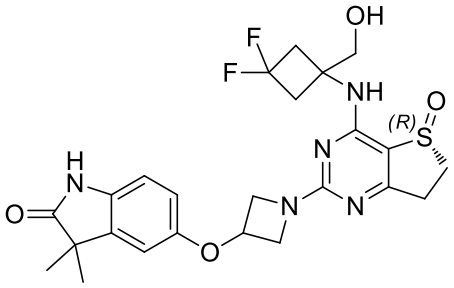


02605-0 MX02605

A solution of (R)-2-chloro-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (10 mg, 0.0331 mmol) and tert-butyl 3-((3-methyl-1H-indol-5-yl)oxy)azetidine-1-carboxylate (10 mg, 0.0309 mmol) in HFP (3 mL) was stirred under microwave conditions at 120°C for 2 hours. Water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19×250 mm, 20 mL/min, UV 254] to afford the white solid product (2.08 mg, 12.8% yield).

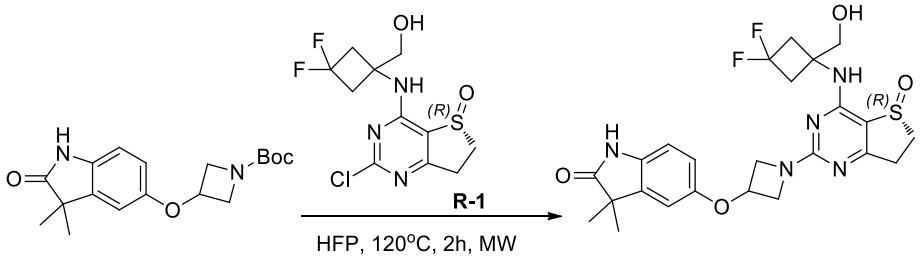
ESI-MS *m/z* calcd for $[C_{23}H_{25}F_2N_5O_3S]$ $[M+H]^+$: 490.0; found: 490.0

^{1}H NMR (400 MHz,DMSO-d_6) δ 10.61 (d, J = 1.6 Hz, 1H), 7.93 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 1.2 Hz, 1H),6.86 (d, J = 2.4 Hz, 1H), 6.71 (dd, J = 8.8, 2.4 Hz, 1H), 5.13 (t, J = 5.6 Hz, 2H),4.48 – 4.44 (m, 2H), 3.97 – 3.95 (m, 2H), 3.68 – 3.66 (m, 2H), 3.48 – 3.39 (m, 1H), 3.25 – 3.17 (m, 1H), 3.02 – 2.79 (m, 6H),2.22 (m, 3H).



MX02606

1. Synthetic scheme:

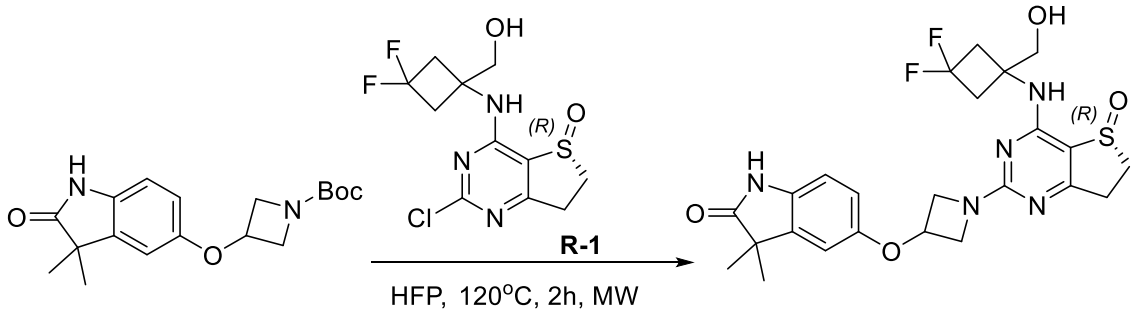


02606-0 **MX02606**

2. Experimental section:

2.1

(R)-5-((1-(4-((3,3-Difluoro-1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)-3,3-dimethylindolin-2-one (MX02606)



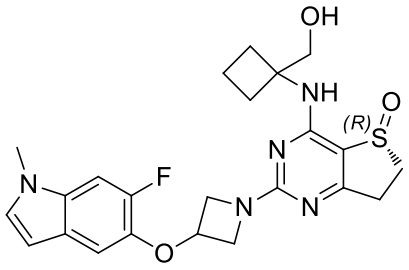
02606-0 **MX02606**

A solution of (R)-2-chloro-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (20 mg, 0.0602 mmol) and tert-butyl 3-((3-methyl-1H-indol-5-yl)oxy)azetidine-1-carboxylate (10 mg, 0.0309 mmol) in HFP (3 mL) was stirred under microwave conditions at 120°C for 2 hours. Water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product. The crude product was purified by preparative HPLC

[MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19×250 mm, 20 mL/min, UV 254] to afford the white solid product (2.27 mg, 14.26% yield).

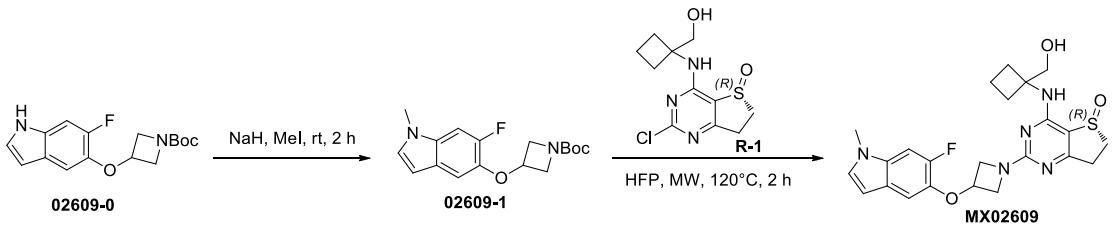
ESI-MS *m/z* calcd for [$C_{24}H_{27}F_2N_5O_4S$] $[M+H]^+$: 519.9; found: 519.9

^{1}H NMR (400 MHz,DMSO-d_6) δ 10.17 (s, 1H), 7.95 (s, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.13 (t, *J* = 6.0 Hz, 2H), 5.06 – 5.01 (m, 1H), 4.46 – 4.42 (m, 2H), 3.93 – 3.90 (m, 2H), 3.68 – 3.66 (m, 1H), 3.47 – 3.39 (m, 1H), 3.24 – 3.17 (m, 1H), 2.99 – 2.83 (m, 6H), 1.24 (s, 6H).



MX02609

1. Synthetic scheme:



02609-0 **02609-1** **MX02609**

2. Experimental section:

2.1

tert-Butyl 3-((6-fluoro-1-methyl-1H-indol-5-yl)oxy)azetidine-1-carboxylate (02609-1)



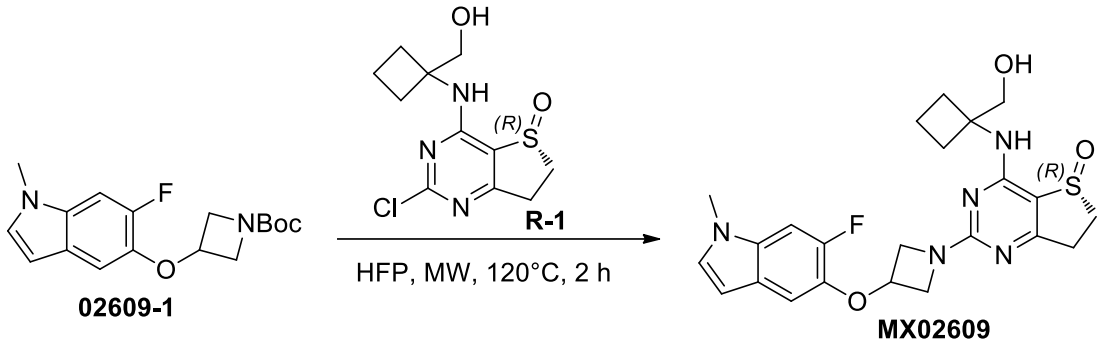
02609-0 **02609-1**

To a solution of tert-butyl 3-((6-fluoro-1H-indol-5-yl)oxy)azetidine-1-carboxylate (30 mg, 0.10 mmol) in DMF (2 mL) at 0°C was added NaH (60%, 5 mg, 0.12 mmol). The mixture was stirred at room temperature for 30 minutes. Then MeI (16 mg, 0.11 mmol) was added, and the mixture was stirred at room temperature for another 2 hours. Water (15 mL) was added to the mixture, and the mixture was extracted with EA (15 mL) twice. The combined organic layers were washed with saturated saturated brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0-8%, Silica gel-CS 20 g, 20 mL/min, UV 254) to afford a colorless oil (21 mg, 68% yield).

ESI-MS *m/z* calcd for $[C_{17}H_{21}FN_2O_3]$ $[M-56+H]^+$: 265.2; found: 265.1

2.2

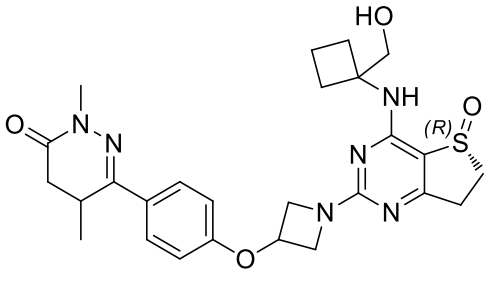
(R)-2-(3-((6-Fluoro-1-methyl-1H-indol-5-yl)oxy)azetidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6, 7-dihydrothieno[3,2-d]pyrimidine-5-oxide (MX02609)



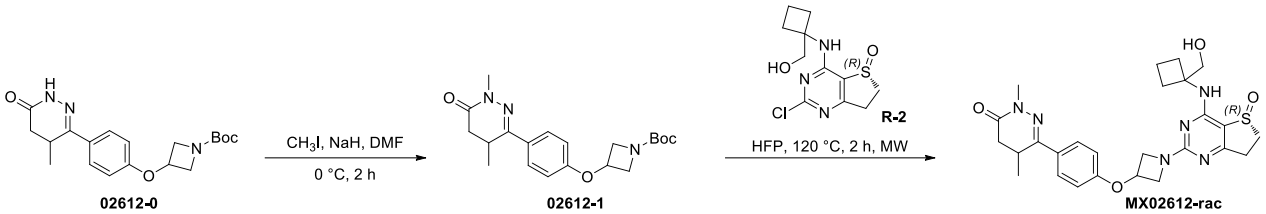
A solution of tert-butyl 3-((6-fluoro-1-methyl-1H-indol-5-yl)oxy)azetidine-1-carboxylate (21 mg, 0.06 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (19 mg, 0.06 mmol) in HFP (2 mL) was stirred under microwave conditions at 120°C for 2 hours. Upon completion of the reaction, the mixture was concentrated under reduced pressure to remove the solvent. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19×250 mm, 20 mL/min, UV 254] to afford the white solid product (6.44 mg, 21% yield).

ESI-MS *m/z* calcd for $[C_{23}H_{26}FN_5O_3S]$ $[M+H]^+$: 472.2; found: 471.6

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (s, 1H), 7.42 (d, J = 12.0 Hz, 1H), 7.29 (d, J = 3.2 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.36 (dd, J = 3.2, 0.4 Hz, 1H), 5.15– 5.10 (m, 1H), 4.84 (t, J = 5.6 Hz, 1H), 4.48 – 4.44 (m, 2H), 4.02 – 3.93 (m, 2H), 3.73 (s, 3H), 3.70 (dd, J = 5.6, 1.6 Hz, 2H), 3.46 – 3.35 (m, 1H), 3.25 – 3.18 (m, 1H), 2.97 – 2.84 (m, 2H), 2.38 – 2.25 (m, 2H), 2.15 – 2.10 (m, 2H), 1.79 – 1.66 (m, 2H).

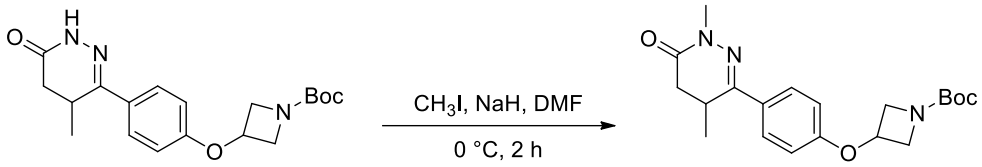


1. Synthetic scheme:



2. Experimental section:

2.1 tert-Butyl 3-(4-(1,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy)azetidine-1-carboxylate(02612-1)

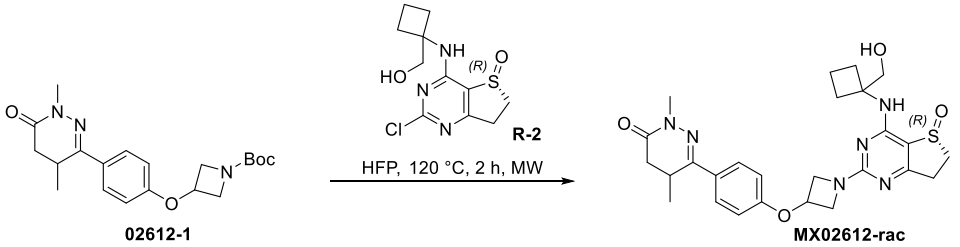


To a solution of tert-butyl 3-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy)azetidine-1-carboxylate (50 mg, 0.14 mmol) in DMF (3 mL) at 0°C was added NaH (60%, 6.7 mg, 0.17 mmol). The mixture was stirred at 0°C for 20 minutes. MeI (22 mg, 0.15 mmol) was then added slowly at 0°C. The mixture was stirred at 0°C under nitrogen protection for 2 hours. Upon completion, ice water (15 mL) was added to the mixture, and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel-CS 12 g, 30 mL/min, Silica, UV 254) to afford a white solid product (33 mg, 63% yield).

ESI-MS *m/z* calcd for $[C_{20}H_{27}N_3O_4]$ $[M+H]^+$: 374.2; found: 373.8

2.2

6-(4-((1-((R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)phenyl)-2,5-dimethyl-4,5-dihydropyridazin-3(2H)-one (MX02612-rac)

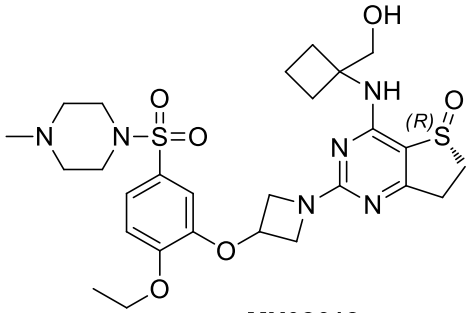


A solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (15 mg, 0.053 mmol) and tert-butyl 3-(4-(1,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy)azetidine-1-carboxylate (20 mg,

0.053 mmol) in HFP (2 mL) was stirred under microwave conditions at 120°C for 2 hours. Upon completion of the reaction, the mixture was concentrated under reduced pressure to remove the solvent. The crude product was purified by preparative HPLC [MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19×250 mm, 20 mL/min, UV 254] to afford the white solid product (6.99 mg, 25% yield).

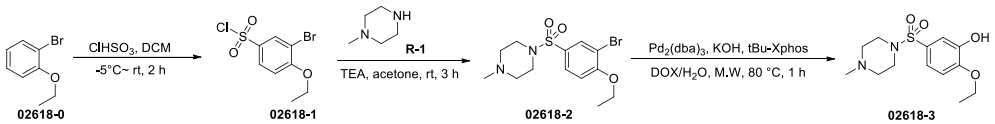
ESI-MS *m/z* calcd for $[C_{26}H_{32}N_6O_4S]$ $[M+H]^+$:525.2; found:524.6

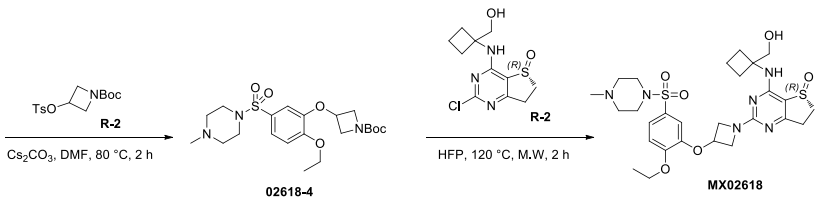
^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 7.79 (d, J = 8.4 Hz, 2H)， 6.96 (d, J = 8.4 Hz, 2H)， 5.19 (br, 1H), 4.51 – 4.47 (m, 2H), 3.95 (br, 2H), 3.75 – 3.70 (m, 2H), 3.47 – 3.36 (m, 2H), 3.32 (s, 3H), 3.30 – 3.22 (m, 1H), 3.00 – 2.88 (m, 2H), 2.73 – 2.67 (m, 1H), 2.34 – 2.24 (m, 3H), 2.16 – 2.11 (m, 2H), 1.81 – 1.70 (m, 2H), 1.07 (d, J = 7.2 Hz, 3H).



MX02618

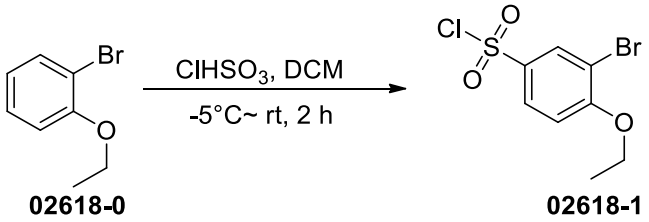
1. Synthetic scheme:





2. Experimental section:

2.1 3-Bromo-4-ethoxyphenyl-1-sulphonyl chloride(02618-1)

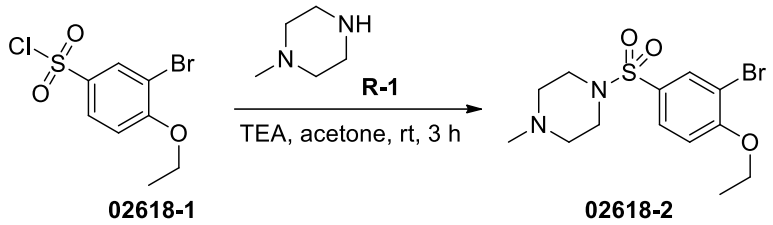


To a solution of 1-bromo-2-ethoxybenzene (1 g, 5.00 mmol) in DCM (10 mL) at -5°C was added chlorosulfonic acid (2 mL) slowly. The mixture was stirred at room temperature for

2 hours. Upon consumption of the starting material, ice water (50 mL) was added, and the mixture was extracted with DCM (50 mL) twice. The combined organic layers were washed with saturated saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford a yellow oil (1.31 g, 88% yield).

ESI-MS *m/z* calcd for $[C_8H_8BrClO_3S]$ $[M+H]^+$: 298.9; found: 298.8

2.2 1-((3-Bromo-4-ethoxyphenyl)sulphonyl)-4-methylpiperazine(02618-2)

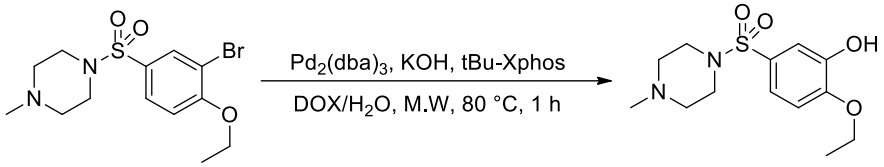


02618-1 02618-2

To a solution of 3-bromo-4-ethoxybenzenesulfonyl chloride (1.31 g, 4.38 mmol) and 1-methylpiperazine (438 mg, 4.38 mmol) in acetone (15 mL) was added TEA (885 mg, 8.76 mmol). The reaction mixture was stirred at room temperature for 3 hours. Upon consumption of the starting material, water (30 mL) was added to the mixture, and the mixture was extracted with EA (30 mL) twice. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product. The crude product was purified by column chromatography (MeOH/DCM = 0/1~1/10, Silica gel-CS 40 g, 40 mL/min, Silica, UV 254) to afford the yellow solid product (1.37 g, 87% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{19}BrN_2O_3S]$ $[M+H]^+$: 363.0; found: 362.8

2.3 2-Ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenol(02618-3)



02618-2 02618-3

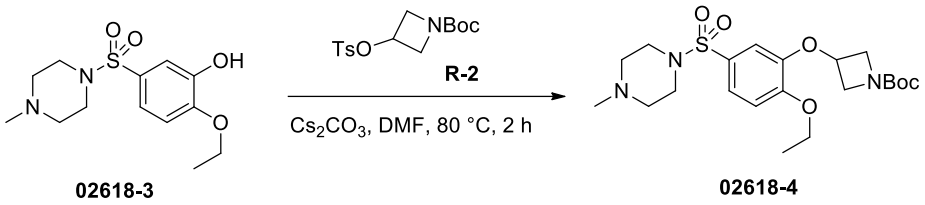
To a solution of 1-((3-bromo-4-ethoxyphenyl)sulfonyl)-4-methylpiperazine (200 mg, 0.55 mmol) in 1,4-dioxane/water (5 mL, v/v=4/1) were added KOH (62 mg, 1.10 mmol), tBu-Xphos (23 mg, 0.055 mmol) and $Pd_2(dba)_3$ (50 mg, 0.055 mmol). The reaction mixture was stirred under microwave conditions at 80°C for 1 hour. Upon consumption of the starting material, water (30 mL) was added to the mixture, and the mixture was extracted with EA (30 mL) twice. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product. The crude product was purified by column chromatography (MeOH/DCM = 0/1~1/10, Silica gel-CS 20

g, 20 mL/min, Silica, UV 254) to afford the white solid product (131 mg, 79% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{20}N_2O_4S]$ $[M+H]^+$: 301.1; found: 300.9

2.4 tert-Butyl 3-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenoxy)azetidin-1-carboxylate

(02618-4)

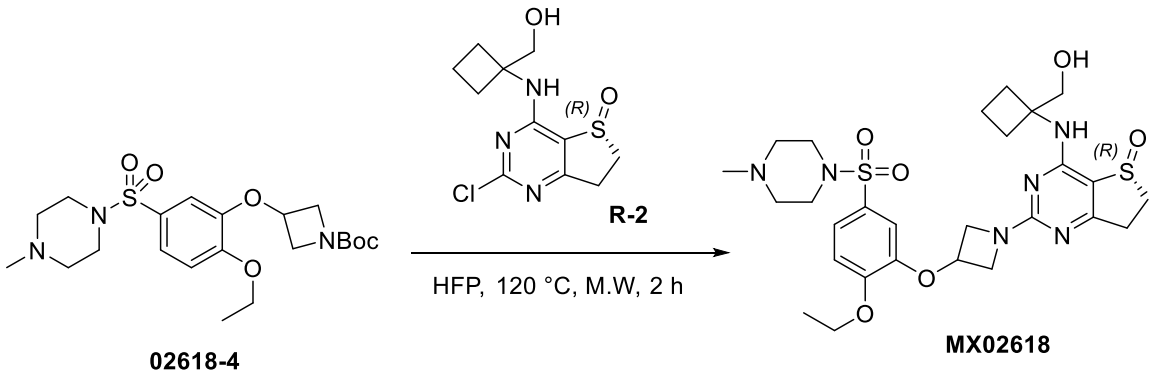


02618-3 02618-4

To a solution of 2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenol (70 mg, 0.23 mmol) and tert-butyl 3-((4-methylphenyl)sulfonyloxy)azetidine-1-carboxylate (76 mg, 0.23 mmol) in DMF (3 mL) was added Cs_2CO_3 (152 mg, 0.47 mmol) at room temperature. The mixture was then stirred at 80 °C for 2 hours. Then water (20 mL) was added and the mixture was extracted with EA (20 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (MeOH/DCM = 0/1 ~ 1/1, Silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid product (98 mg, 92% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{33}N_3O_6S]$ $[M+H]^+$: 456.2; found: 455.8

2.5(R)-2-(3-(2-Ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenoxy)azetidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02618)



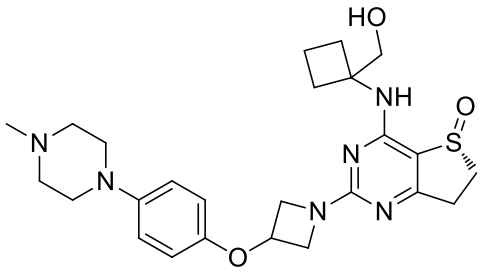
02618-4 MX02618

A solution of tert-butyl 3-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenoxy)azetidine-1-carboxylate (30 mg, 0.06 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (19 mg, 0.06 mmol) in HFP (2 mL) was stirred under microwave conditions at 120 °C for 2 hours. Then, water (10 mL) was added to the mixture and the mixture was extracted with DCM (10 mL)

twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid compound (12.05 mg, 30% yield).

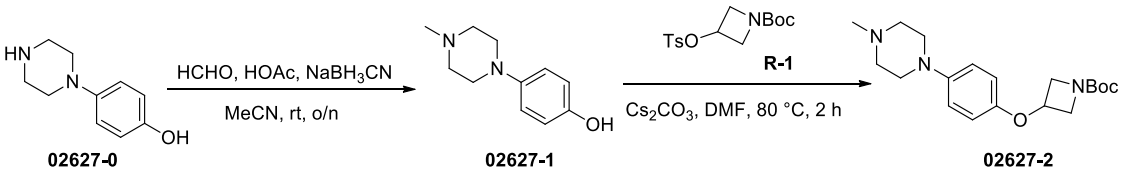
ESI-MS *m/z* calcd for $[C_{27}H_{38}N_6O_6S_2]$ $[M+H]^+$: 607.2; found: 606.7

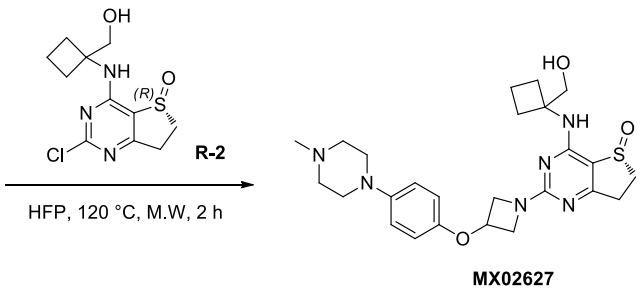
^{1}H NMR (400 MHz,DMSO-d_6) δ 7.48 (s, 1H), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 5.23 – 5.18 (m, 1H), 4.85 (t, *J* = 5.6 Hz, 1H), 4.44 (dd, *J* = 10.0, 6.4 Hz, 2H), 4.15 (q, *J* = 6.8 Hz, 2H), 4.05 – 3.85 (m, 2H), 3.72 – 3.65 (m, 2H), 3.46 – 3.35 (m, 1H), 3.25 – 3.18 (m, 1H), 2.98 – 2.85 (m, 6H), 2.39 – 2.26 (m, 6H), 2.15 (s, 3H), 2.14 –2.08 (m, 2H)， 1.82 –1.67 (m, 2H), 1.37(t, *J* = 7.2 Hz, 3H).



MX02627

1. Synthetic scheme:



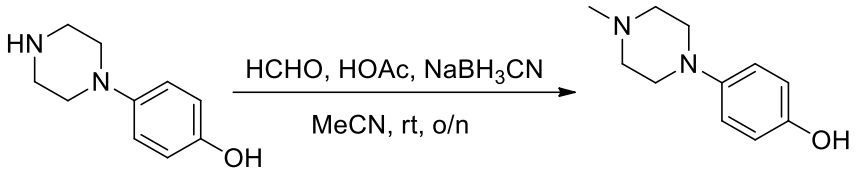


MX02627

2. Experimental section:

2.1

4-(4-Methylpiperazin-1-yl)phenol(02627-1)



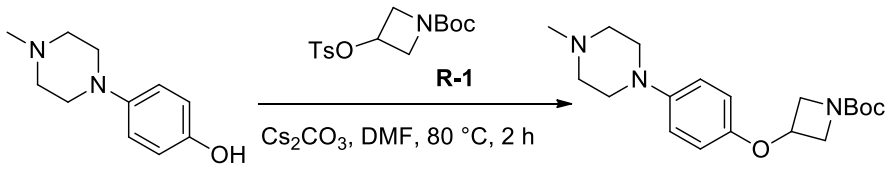
02627-0 02627-1

To a solution of 4-(piperazin-1-yl)phenol (150 mg, 0.84 mmol) in MeCN (2 mL) was added acetic acid (0.5 mL), 37% formaldehyde solution (126 mg, 4.21 mmol), and $NaBH_3CN$ (106 mg, 1.68 mmol) at 0 °C. The mixture was slowly warmed to room temperature and stirred overnight until the starting material was consumed. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl (20 mL) and extracted with EA (15 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0~100%, Silica gel, 12 g, 15 mL/min, UV 254) to afford the white solid product (103 mg, 64% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{16}N_2O]$ $[M+H]^+$: 193.1; found: 193.0

2.2

tert-Butyl 3-(4-(4-methylpiperazin-1-yl)phenoxy)azetidin-1-carboxylate (02627-2)



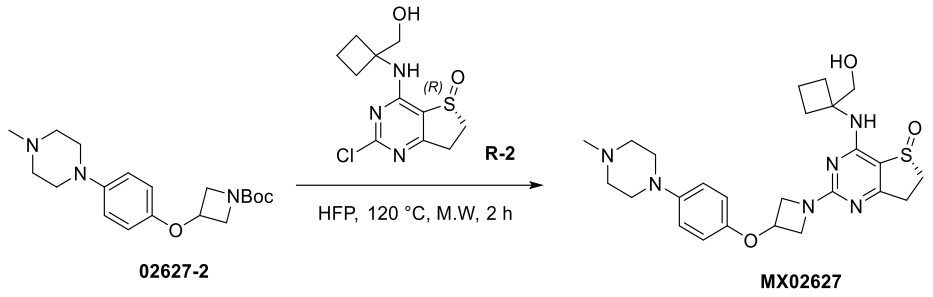
02627-1 02627-2

To a solution of 4-(4-methylpiperazin-1-yl)phenol (103 mg, 0.53 mmol) in DMF (3 mL) and Cs_2CO_3 (345 mg, 1.06 mmol) was added tert-butyl 3-((4-methylphenyl)sulfonyloxy)azetidine-1-carboxylate (175 mg, 0.53 mmol). The reaction mixture was stirred at 80 °C for 2 hours. Then, the solvent was removed under reduced pressure. Water (50 mL) was added, and the mixture was extracted with EA (30 mL) twice. The combined organic layers were washed with saturated saturated brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0~50%, Silica gel, 12 g, 20 mL/min, UV 254) to afford the yellow solid product (87 mg, 47% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{29}N_3O_3]$ $[M+H]^+$: 348.2; found: 348.0

2.3

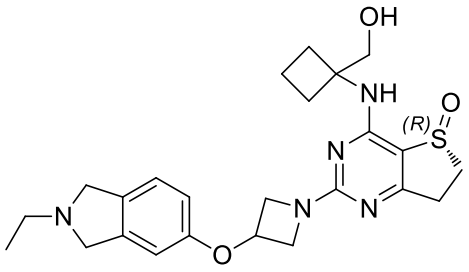
(R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(3-(4-(4-methylpiperazin-1-yl)phenoxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02627)



A solution of tert-butyl 3-(4-(4-methylpiperazin-1-yl)phenoxy)azetidine-1-carboxylate (30 mg, 0.08 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (25 mg, 0.08 mmol) in HFP (2 mL) was stirred at 120 °C under microwave conditions for 2 hours. Then, water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid compound (3.52 mg, 8% yield).

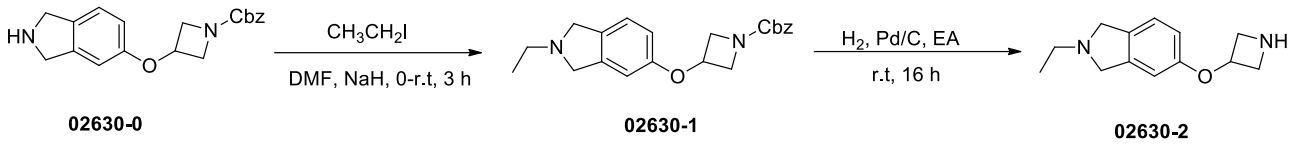
ESI-MS *m/z* calcd for $[C_{25}H_{34}N_6O_3S]$ $[M+H]^+$: 499.2; found: 499.2

^{1}H NMR (400 MHz,DMSO-d_6) δ 7.45 (s, 1H), 6.91 – 6.87 (m, 2H), 6.77– 6.74 (m, 2H), 5.04 – 5.00 (m, 1H), 4.85 (t, J = 5.6 Hz, 1H), 4.41 (dd, J = 9.6, 6.4 Hz, 2H), 3.95 – 3.84 (m, 2H), 3.70 – 3.67 (m, 2H), 3.45 – 3.36 (m, 1H), 3.25 – 3.17 (m, 1H), 3.01 (t, J = 5.2 Hz, 4H), 2.96 – 2.84 (m, 2H), 2.44 (t, J = 4.8 Hz, 4H), 2.38 – 2.25 (m, 2H), 2.21 (s, 3H) , 2.14 –2.10 (m, 2H)，1.79 –1.68 (m, 2H).

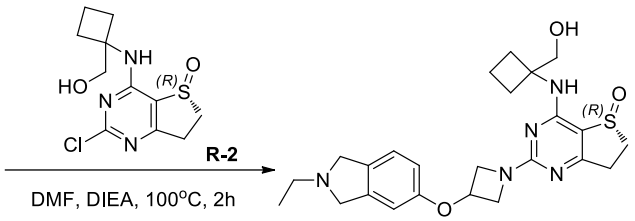


MX02630

1. Synthetic scheme:



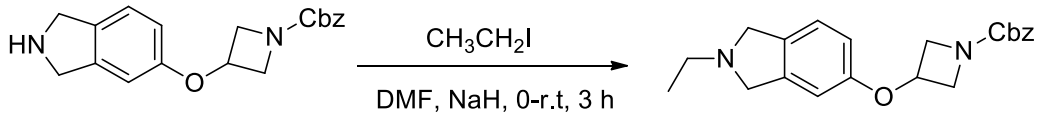
02630-0 02630-1 02630-2



MX02630

2. Experimental section:

2.1 Benzyl 3-((2-ethylisoindolin-5-yl)oxy)azetidin-1-carboxylate (02630-1)

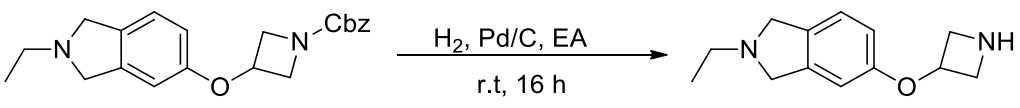


02630-0 02630-1

To a solution of NaH (60%, 22.0 mg, 0.54 mmol) in DMF (3.0 mL) was added Benzyl 3-(isoindolin-5-yloxy)azetidine-1-carboxylate (88.0 mg, 0.27 mmol) at 0 °C,. The reaction mixture was stirred under argon protection at 0 °C for 0.5 hours. Then, a solution of EtI (92.3 mg, 0.54 mmol) in DMF (1 mL) was added, and the mixture was stirred at room temperature for 3 hours. The reaction was quenched with water (10 mL) and extracted with EA (10 mL) three times. The combined organic layers were washed with saturated saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (MeOH/DCM = 0~1/10, Silica gel, 12 g, 30 mL/min, UV 254) to afford the colorless oil product (28.0 mg, 29.3% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{24}N_2O_3]$ $[M+H]^+$:353.2; found:353.0.

2.2 5-(Azetidin-3-yloxy)-2-ethylisoindoline (02630-2)



02630-1 02630-2

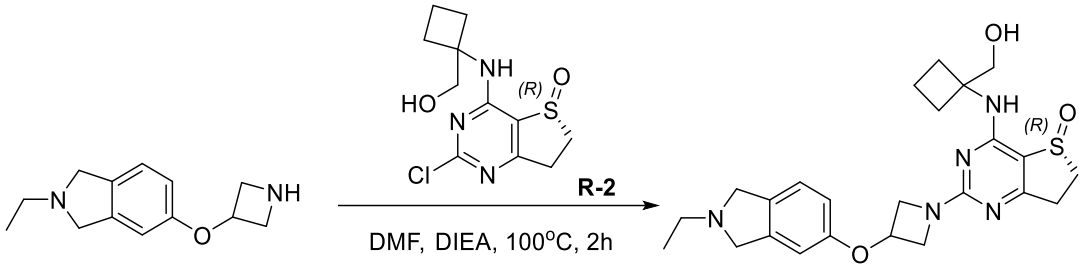
To a solution of Benzyl 3-((2-ethylisoindolin-5-yl)oxy)azetidine-1-carboxylate (28.0 mg, 0.08 mmol) in EA (5.0 mL) was added Pd/C (5.0 mg). The mixture was stirred at room temperature for 16 hours under a hydrogen atmosphere. Then, the mixture was filtered through

Celite, and the filtrate was concentrated under reduced pressure to afford the colorless oil product (20.0 mg, 100.0% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{18}N_2O]$ $[M+H]^+$:219.1; found:219.2

2.3

(R)-2-(3-((2-Ethylisoindolin-5-yl)oxy)azetidin-1-yl)-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02630)

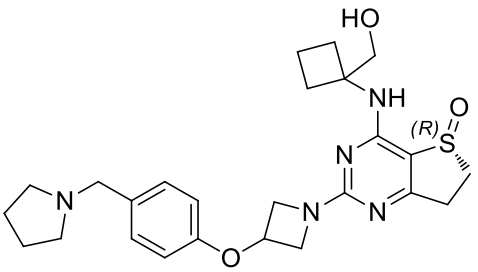


02630-2 MX02630

To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (26.3 mg, 0.092 mmol) in DMF (3 mL) was added 5-(azetidin-3-yloxy)-2-ethylisoindoline (20.0 mg, 0.092 mmol) and DIEA (100.8 mg, 0.78 mmol). The mixture was stirred at 100 °C for 2 hours. After completion, the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC ($MeCN/H_2O$ (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (8.0 mg, 18.6% yield).

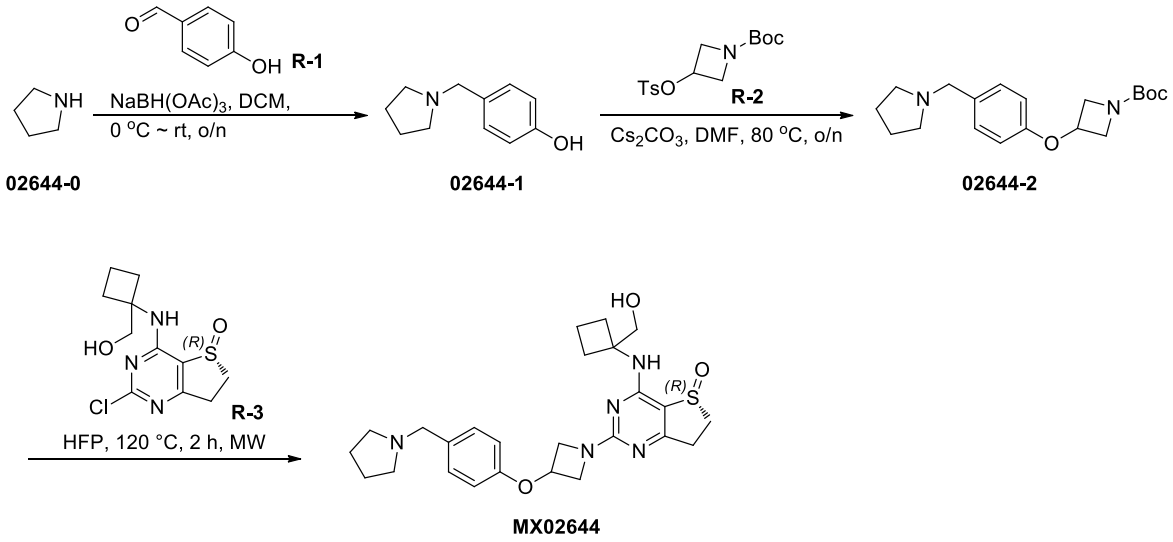
ESI-MS *m/z* calcd for $[C_{24}H_{31}N_5O_3S]$ $[M+H]^+$: 470.2; found: 470.0

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (s, 1H), 7.15(d, J = 8.4 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 8.4, 2.4 Hz, 1H), 5.10 – 5.05 (m, 1H), 4.88 (t, J = 15.6 Hz, 1H), 4.46 – 4.42 (m, 2H), 3.90 – 3.89 (m, 2H), 3.77 (d, J = 5.6 Hz,4H), 3.72 –3.66 (m, 2H), 3.26 –3.14 (m, 2H), 2.97 –2.85 (m, 2H), 2.69 –2.64 (m, 2H), 2.37 –2.24 (m, 2H), 2.15 –2.10 (m, 2H), 1.79 – 1.68 (m, 2H)， 1.09 (t, J = 7.2 Hz, 3H).



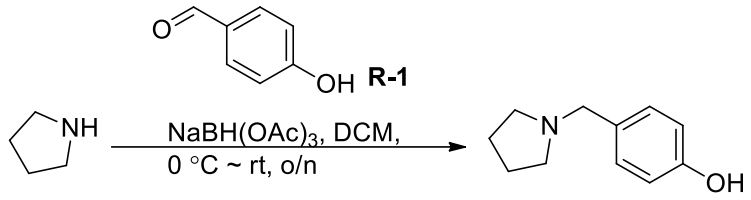
MX02644

1. Synthetic scheme:



2. Experimental section:

2.1 4-(Pyrrolidin-1-ylmethyl)phenol(02644-1)

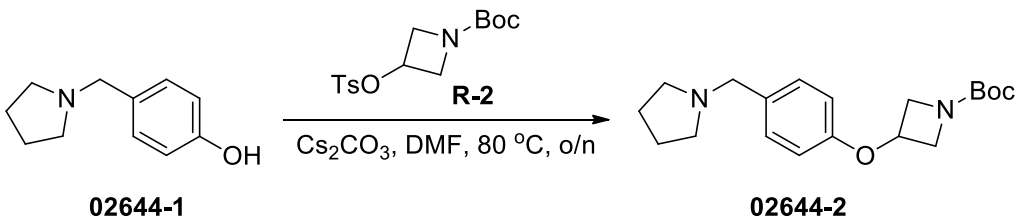


To a solution of pyrrole (200 mg, 2.82 mmol) and 4-hydroxybenzaldehyde (312 mg, 2.56 mmol) in DCM (10 mL) was added $NaBH(OAc)_3$ (814 mg, 3.84 mmol) in portions at 0 °C. The mixture was stirred at room temperature under nitrogen protection overnight until the starting material was consumed. Ice water (15 mL) was added, and the pH was adjusted to 9 with $NaHCO_3$. The mixture was extracted with DCM (30 mL) three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 12 g, 30 mL/min, UV 254) to afford the white solid product (336 mg, 74% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{15}NO]$ $[M+H]^+$: 178.1; found: 178.2

2.2

tert-Butyl 3-(4-(pyrrolidin-1-ylmethyl)phenoxy)azetidin-1-carboxylate (02644-2)

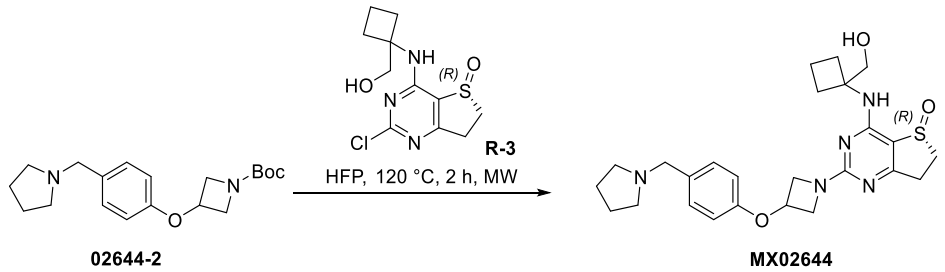


To a solution of 4-(pyrrolidin-1-ylmethyl)phenol (100 mg, 0.56 mmol) and Cs_2CO_3 (548 mg, 1.68 mmol) in DMF (3 mL) was added tert-butyl 3-((4-methylphenyl)sulfonyloxy)azetidine-1-carboxylate (183 mg, 0.56 mmol) at room temperature. The mixture was stirred at 80 °C overnight. Water (20 mL) was added, and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/4, Silica gel, 20 g, 30 mL/min, UV 254) to afford the yellow solid product (132 mg, 71% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{28}N_2O_3]$ $[M+H]^+$: 333.2; found: 333.2

2.3

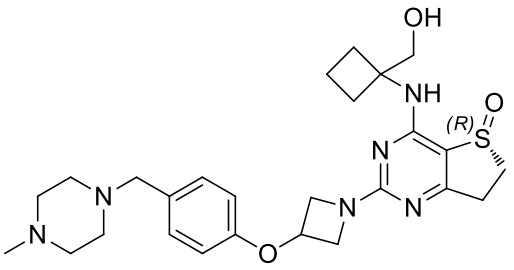
(R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(3-(4-(pyrrolidin-1-ylmethyl)phenoxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02644)



A solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (26 mg, 0.09 mmol) and tert-butyl 3-(4-(pyrrolidin-1-ylmethyl)phenoxy)azetidine-1-carboxylate (30 mg, 0.09 mmol) in HFP (2 mL) was stirred at 120 °C under microwave conditions for 2 hours. After completion, the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (10.4 mg, 23.9% yield).

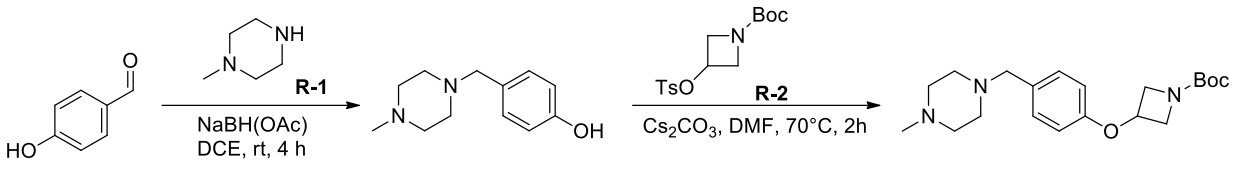
ESI-MS *m/z* calcd for $[C_{25}H_{33}N_5O_3S]$ $[M+H]^+$:484.2; found:483.8

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (s, 1H), 7.22 (d, J = 8.4 Hz, 2H)， 6.81 (d, J = 8.4 Hz, 2H)， 5.11 – 5.06 (m, 1H), 4.84 (t, J = 5.6 Hz, 1H)， 4.44 (dd, J = 10.0, 6.4 Hz, 2H)， 3.91 (br, 2H)， 3.69 (d, J = 7.2 Hz, 2H), 3.49 (s, 2H), 3.43 – 3.37 (m, 1H), 3.25 – 3.17 (m, 1H), 2.97 – 2.84 (m, 2H), 2.39 – 2.25 (m, 6H), 2.15 – 2.09 (m, 2H), 1.79 – 1.65 (m, 6H).

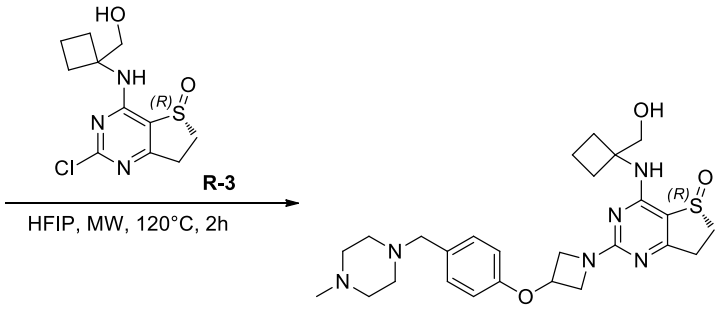


MX02645

1. Synthetic scheme:



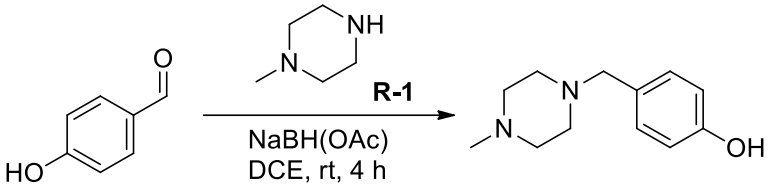
02645-0 **02645-1** **02645-2**



MX02645

2. Experimental section:

2.1 4-((4-Methylpiperazin-1-yl)methyl)phenol(02645-1)



02645-0 **02645-1**

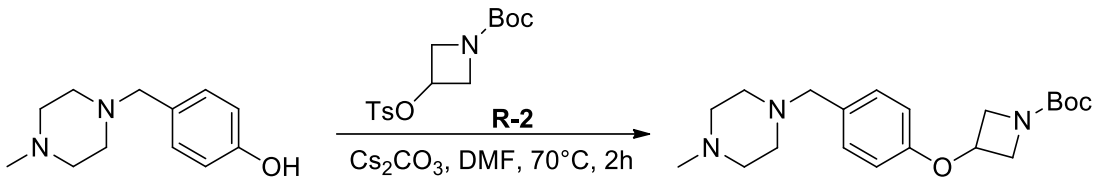
To a solution of 4-hydroxybenzaldehyde (200 mg, 1.64 mmol) in DCE (5 mL) was added N-methylpiperazine (164 mg, 1.64 mmol) and $NaBH(OAc)_3$ (521 mg, 3.07 mmol) at 0 °C. The mixture was stirred at room temperature under nitrogen protection for 4 hours until the starting material was consumed. Water (20 mL) was added, and the mixture was extracted with EA (50 mL) three times. The combined organic layers were washed with saturated saturated brine (50

mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (MeOH/EA = 0/1~10/1, Silica gel, 12 g, 25 mL/min, UV 254) to afford the colorless oil product (156 mg, 46% yield).

ESI-MS *m/z* calcd for $[C_{12}H_{18}N_2O]$ $[M+H]^+$: 207.1; found: 207.3

2.2

tert-Butyl 3-(4-((4-methylpiperazin-1-yl)methyl)phenoxy)azetidin-1-carboxylate(02645-2)



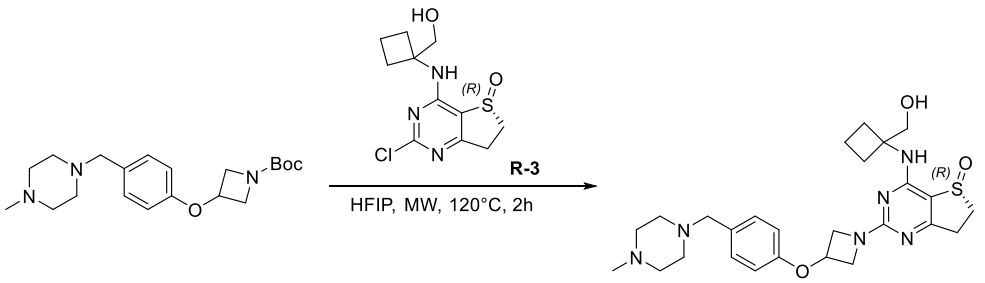
02645-1 **02645-2**

To a solution of 4-((4-methylpiperazin-1-yl)methyl)phenol (150 mg, 0.73 mmol) in DMF (5 mL) was added tert-butyl 3-((4-methylphenyl)sulfonyloxy)azetidine-1-carboxylate (238 mg, 0.73 mmol) and Cs_2CO_3 (475 mg, 1.46 mmol). The mixture was stirred under nitrogen protection at 70 °C for 2 hours until the starting material was consumed. The mixture was then concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the pale yellow oil product (44 mg, 17% yield).

ESI-MS *m/z* calcd for $[C_{20}H_{31}N_3O_3]$ $[M+H]^+$: 362.2; found: 361.9

2.3

(R)-4-((1-(hydroxymethyl)cyclobutyl)amino)-2-(3-(4-((4-methylpiperazin1-yl)methyl)phenoxy)azetidin-1-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02645)



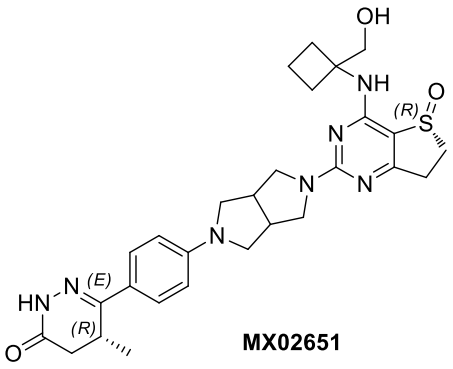
02645-2 **MX02645**

To a solution of tert-butyl 3-(4-((4-methylpiperazin-1-yl)methyl)phenoxy)azetidine-1-carboxylate (44 mg, 0.21 mmol) in HFIP (3 mL) was added (R)-2-chloro-4-((1-

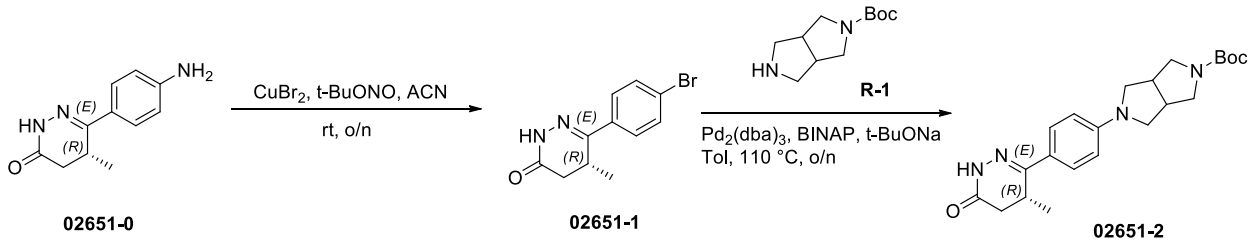
(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (35 mg, 0.21 mmol). The mixture was stirred under nitrogen protection at 120 °C under microwave conditions for 2 hours until the starting material was consumed. The reaction mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (3.24 mg, 3% yield).

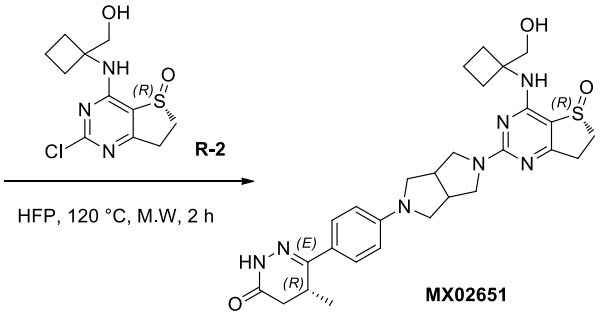
ESI-MS *m/z* calcd for $[C_{26}H_{36}N_6O_3S]$ $[M+H]^+$: 513.3; found: 513.0

^{1}H NMR (400 MHz,CD_3OD) δ7.27 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.11 – 5.08 (m, 1H), 4.53 – 4.49 (m, 2H), 4.05 – 4.03 (m, 2H), 3.95 – 3.86 (m, 2H), 3.59 – 3.53 (m, 1H), 3.48 – 3.47 (m, 2H), 3.41 – 3.33 (m, 1H), 3.13 – 3.05 (m, 2H), 2.60 – 2.22 (m, 15H), 1.92 – 1.84 (m, 2H).



1. Synthetic scheme:

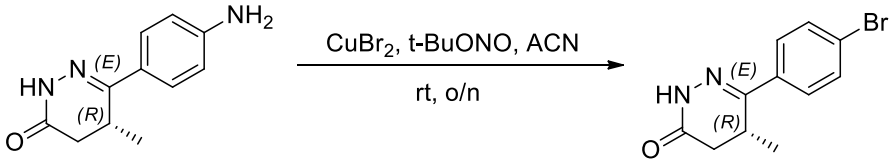




2. Experimental section:

2.1

(R)-6-(4-Bromophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one(02651-1)



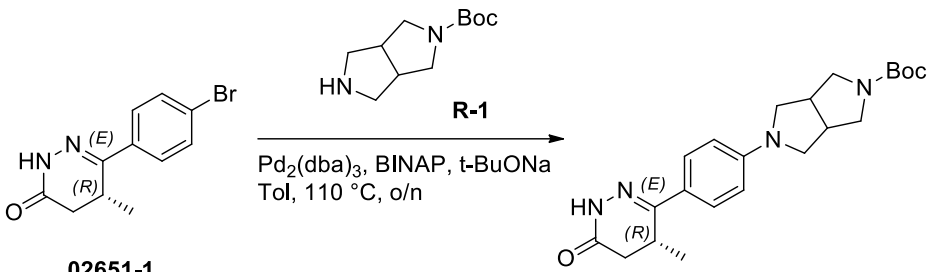
02651-0 02651-1

To a solution of (R)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (500 mg, 2.45 mmol) in MeCN (10 mL) was added $CuBr_2$ (550 mg, 2.45 mmol) and tert-butyl nitrite (375 mg, 3.67 mmol) at room temperature. The mixture was stirred at room temperature overnight. Ice water (50 mL) was added, and the mixture was extracted with EA (50 mL) twice. The combined organic layers were washed with saturated saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 40 g, 40 mL/min, UV 254) to afford the yellow solid product (370 mg, 56% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{11}BrN_2O]$ $[M+H]^+$: 267.0; found: 267.1

2.2

tert-Butyl 5-(4-((R)-4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate(02651-2)



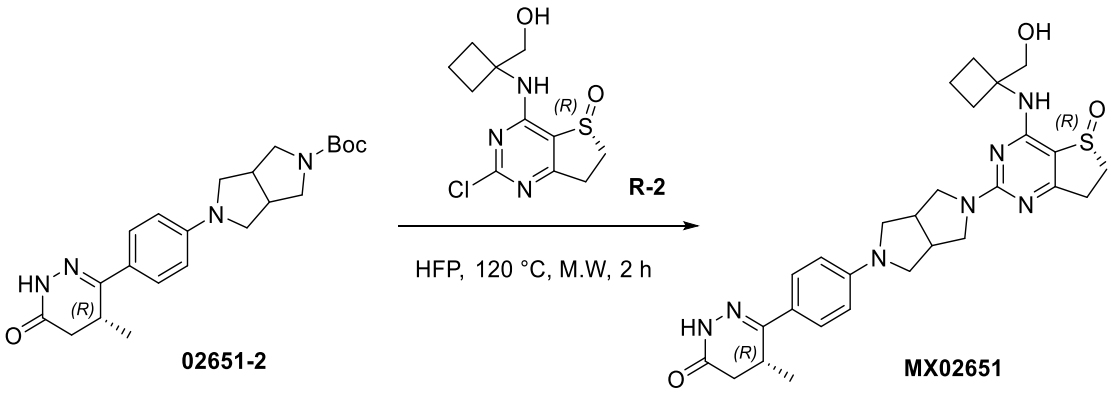
02651-1 02651-2

To a solution of (R)-6-(4-bromophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (100 mg, 0.37 mmol) in Toluene (3 mL) was added tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (79 mg, 0.37 mmol), t-BuONa (72 mg, 0.75 mmol), BINAP (25 mg, 0.04 mmol) and $Pd_2(dba)_3$ (36 mg, 0.04 mmol). The mixture was stirred at 110 °C under argon protection overnight until the starting material was consumed. After the starting material was consumed, water (30 mL) was added, and the mixture was extracted with EA (30 mL) twice. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 20 g, 20 mL/min, UV 254) to afford the yellow solid product (25 mg, 17% yield).

ESI-MS *m/z* calcd for [$C_{22}H_{30}N_4O_3$] [M+H]$^+$: 399.2; found: 398.9

2.3

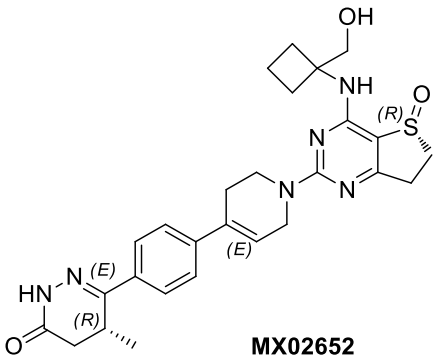
(5R)-6-(4-(5-((R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)phenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (MX02651)



A solution of tert-butyl 5-(4-((R)-4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (25 mg, 0.06 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (18 mg, 0.06 mmol) in HFP (2 mL) was stirred at 120 °C under microwave conditions for 2 hours. Then, water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (2.15 mg, 6% yield).

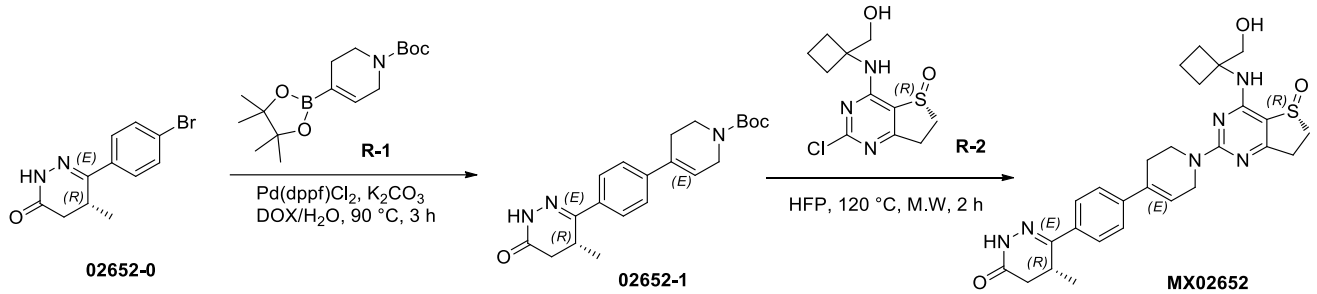
ESI-MS *m/z* calcd for [$C_{28}H_{35}N_7O_3S$] [M+H]$^+$: 550.3; found: 549.7

^{1}H NMR (400 MHz,DMSO-d_6) δ 10.69 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.27 (s, 1H), 6.58 (d, J = 9.2 Hz, 2H), 4.83(t, J = 5.6 Hz, 1H), 3.82 – 3.76 (m, 2H), 3.72 (d, J = 5.6 Hz, 2H), 3.60 – 3.51 (m, 2H), 3.48 – 3.33 (m, 4H), 3.06 – 3.38 (m, 5H), 2.94 – 2.82 (m, 2H), 2.67 – 2.59 (m, 1H), 2.42 – 2.28 (m, 2H), 2.20 –2.12 (m, 3H)，1.81 –1.71 (m, 2H), 1.03(d, J = 7.2 Hz, 3H).



MX02652

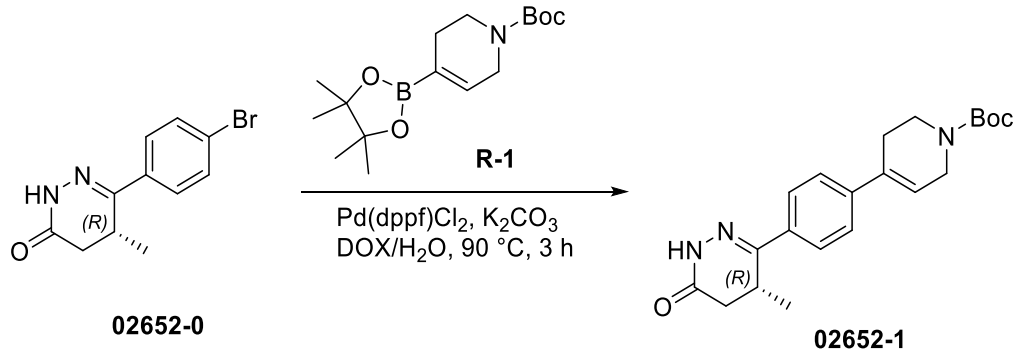
1. Synthetic scheme:



2. Experimental section:

2.1

tert-Butyl(R)-4-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (02652-1)



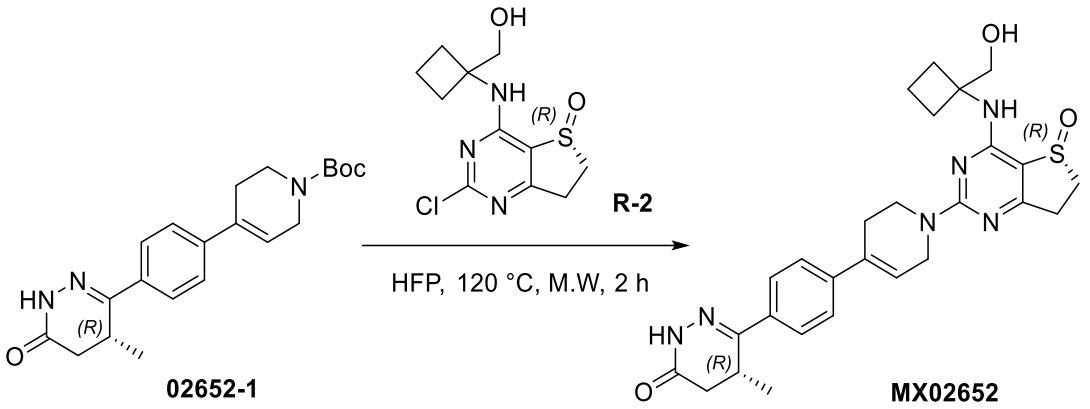
To a solution of (R)-6-(4-bromophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (70 mg, 0.26 mmol) in 1,4-dioxane/H_2O (2.4 mL, v/v=5/1) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (99 mg, 0.32 mmol), K_2CO_3 (76 mg, 0.78 mmol), and $Pd(dppf)Cl_2$ (18 mg, 0.026 mmol). The mixture was stirred at 90 °C under argon protection for 3 hours until the starting material was consumed. After the starting material was consumed, water (30 mL) was added, and the mixture was extracted with EA (30 mL) twice. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 20 g, 20

mL/min, UV 254) to afford the yellow solid product (89 mg, 92% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{27}N_3O_3]$ $[M+H]^+$: 370.2; found: 369.9

2.2

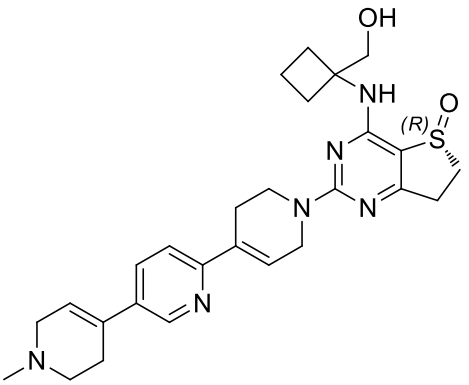
(R)-6-(4-(1-((R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (MX02652)



A solution of (R)-4-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (40 mg, 0.10 mmol) and (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (29 mg, 0.10 mmol) in HFP (2 mL) was stirred at 120 °C under microwave conditions for 2 hours. Then, water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (10.11 mg, 18% yield).

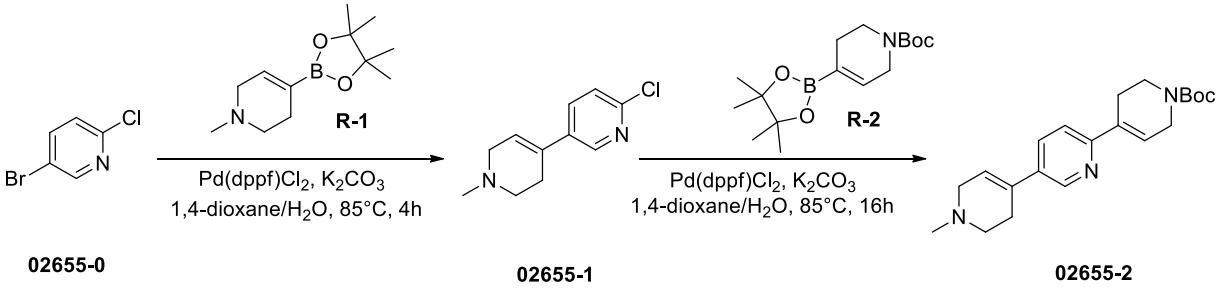
ESI-MS *m/z* calcd for $[C_{27}H_{32}N_6O_3S]$ $[M+H]^+$: 521.2; found: 520.6

^{1}H NMR (400 MHz,DMSO-d_6) δ 10.96 (s, 1H) , 7.76 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.39 (s, 1H), 6.40 – 6.36 (m, 1H), 4.85 (t, J = 5.6 Hz, 1H), 4.38 – 4.36 (m, 2H), 3.99 (t, J = 5.2 Hz, 2H), 3.97 – 3.75 (m, 2H), 3.47 – 3.35 (m, 2H), 3.30 – 3.18 (m, 1H), 2.98 – 2.84 (m, 2H), 2.73 – 2.67 (m, 1H), 2.68 –2.66 (m, 2H)，2.43 –2.18 (m, 5H), 1.84 –1.73 (m, 2H), 1.07(d, J = 7.2 Hz, 3H).

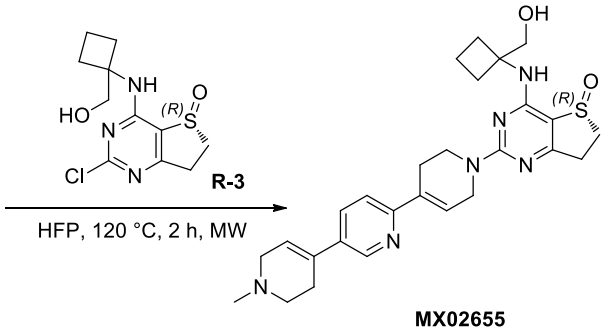


MX02655

1. Synthetic scheme:



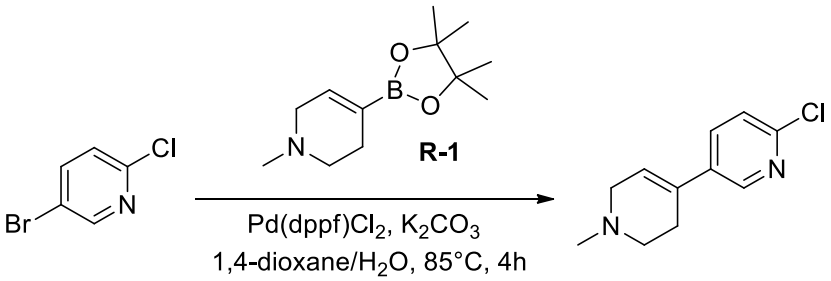
02655-0 **02655-1** **02655-2**



MX02655

2. Experimental section:

2.1 6-Chloro-1'-methyl-1',2',3',6'-tetrahydro-3,4'-bipyridine(02655-1)



02655-0 **02655-1**

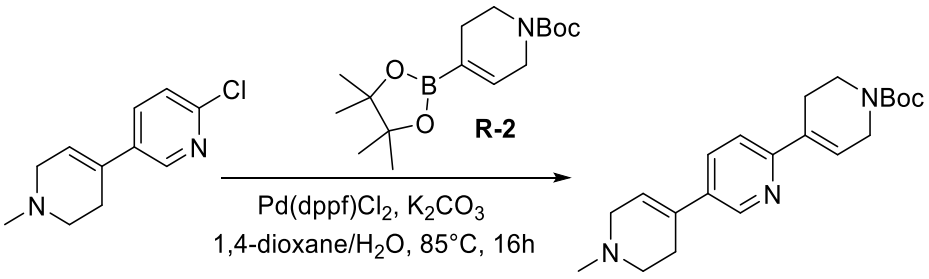
To a solution of 5-bromo-2-chloropyridine (192.4 mg, 1.0 mmol) in 1,4-dioxane/H_2O (6.0 mL, v/v=5/1) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (223.1 mg, 1.0 mmol), K_2CO_3 (414.6 mg, 3.0 mmol), and $Pd(dppf)Cl_2$ (73.1

mg, 0.1 mmol). The mixture was stirred at 85 °C under nitrogen protection for 4 hours until the starting material was consumed. After the starting material was consumed, water (20 mL) was added, and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (MeOH/DCM = 0/1~1/10, Silica gel, 40 g, 40 mL/min, UV 254) to afford the yellow solid product (128.0 mg, 61.5% yield).

ESI-MS *m/z* calcd for $[C_{11}H_{13}ClN_2]$ $[M+H]^+$: 209.1; found: 209.0

2.2

tert-Butyl 1''-methyl-1'',2'',3,3'',6,6''-hexahydro-[4,2':5',4''-terpyridine]-1(2H)-carboxylate (02655-2)



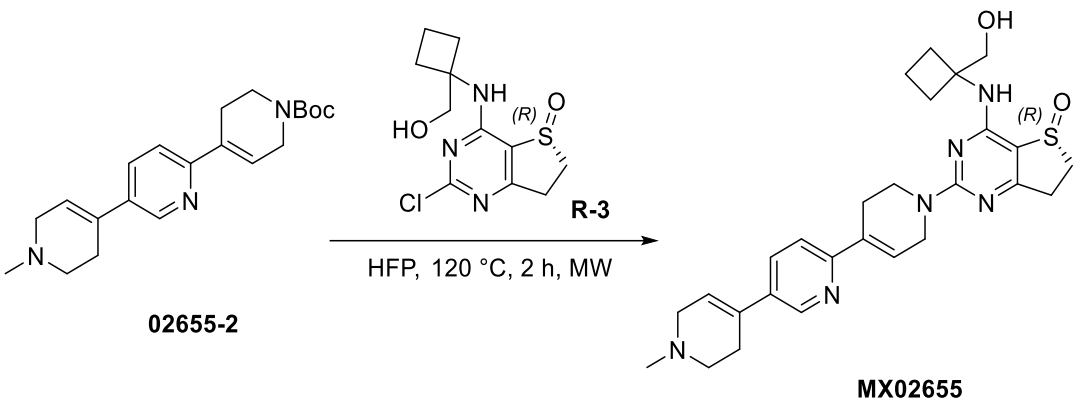
02655-1 **02655-2**

To a solution of 6-chloro-1'-methyl-1',2',3',6'-tetrahydro-3,4'-bipyridine (128.0 mg, 0.615 mmol) in 1,4-dioxane/H_2O (6.0 mL, v/v=5/1) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (190.3 mg, 0.615 mmol), K_2CO_3 (254.0 mg, 1.845 mmol), and $Pd(dppf)Cl_2$ (44.0 mg, 0.06 mmol). The mixture was stirred at 85 °C under nitrogen protection for 16 hours until the starting material was consumed. After the starting material was consumed, water (20 mL) was added, and the mixture was extracted with EA (20 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (MeOH/DCM = 0/1~1/10, Silica gel, 40 g, 40 mL/min, UV 254) to afford the yellow solid product (85.0 mg, 39.0% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{29}ClN_3O_2]$ $[M+H]^+$: 356.2; found: 356.0

2.3

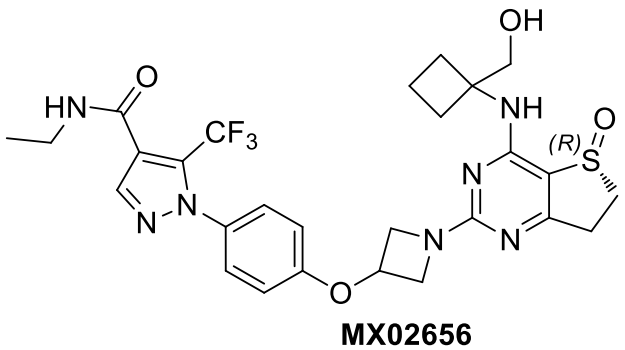
(R)-4-((1-(Hydroxymethyl)cyclobutyl)amino)-2-(1''-methyl-1'',2'',3,3'',6,6''-hexahydro-[4,2':5',4''-terpyridin]-1(2H)-yl)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (MX02655)



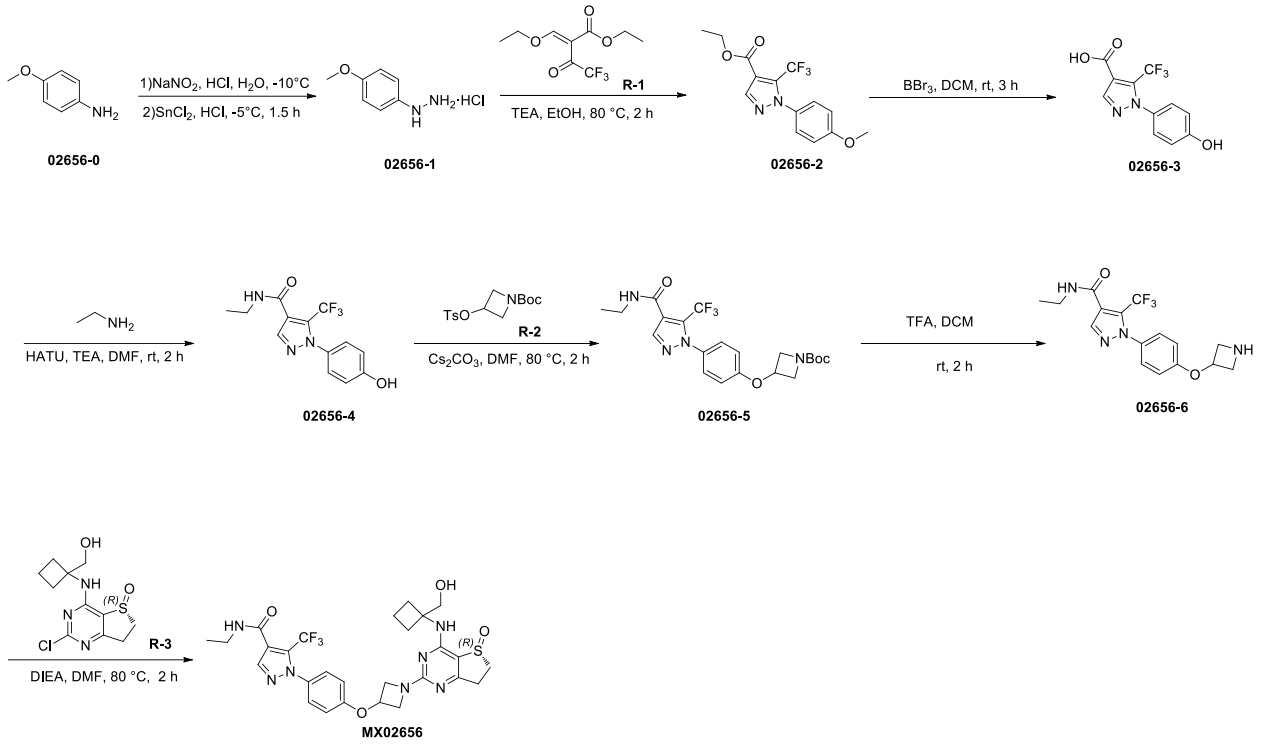
A solution of (R)-2-chloro-4-((3,3-difluoro-1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (29.0 mg, 0.1 mmol) and tert-butyl 1''-methyl-1'',2'',3'',5,6,6''-hexahydro-[4,2':5',4''-terpyridine]-1(2H)-carboxylate (36.0 mg, 0.1 mmol) in HFP (3 mL) was stirred at 120 °C under microwave conditions for 2 hours. Then, water (10 mL) was added to the mixture, and the mixture was extracted with DCM (10 mL) twice. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (12.0 mg, 24.0% yield).

ESI-MS *m/z* calcd for $[C_{27}H_{34}N_6O_2S]$ $[M+H]^+$: 507.2; found: 506.8

^{1}H NMR (400 MHz,DMSO-d_6) δ8.63 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 6.0, 2.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 6.79 (s, 1H), 6.29 (s, 1H),4.86 (t, J = 5.6 Hz, 1H), 4.41 (s, 2H), 3.97 (t, J = 5.2 Hz, 2H), 3.76 – 3.75 (m, 2H), 3.47 – 3.34 (m, 1H), 3.29 – 3.18 (m, 1H), 3.02 (d, J = 2.8 Hz, 2H), 3.00 – 2.92 (m, 1H), 2.89 – 2.84 (m, 1H)，2.67 –2.56 (m, 5H)，2.40 – 2.32 (m, 3H), 2.28 (s, 3H)，2.22 –2.17 (m, 2H)，1.83 –1.76 (m, 2H).

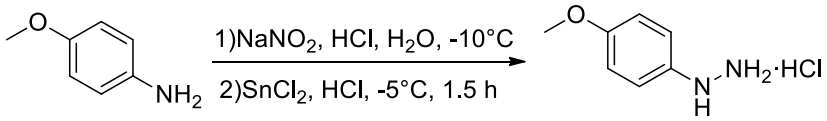


1. Synthetic scheme:



2. Experimental section:

2.1 (4-Methoxyphenyl)hydrazine hydrochloride(02656-1)



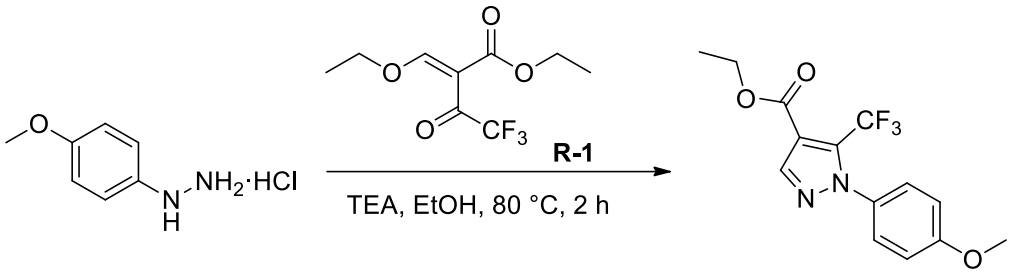
02656-0 **02656-1**

To a solution of 4-methoxyaniline (4.0 g, 32.52 mmol) in conc. HCl/H_2O (30 mL, v/v=1/1) was added $NaNO_2$ (2.24 g, 32.52 mmol) at -10 °C. The mixture was stirred at -10 °C for 45 minutes. Then, an aqueous solution of $SnCl_2 \cdot 2H_2O$ (14.66 g, 65.04 mmol) was slowly added dropwise. The mixture was stirred at room temperature for 2 hours. The mixture was filtered, and the filter cake was washed with Et_2O. Drying under vacuum afforded the brown solid product (2.67 g, 47.1% yield).

ESI-MS *m/z* calcd for $[C_7H_{10}N_2O]$ $[M+H]^+$: 139.1; found: 139.3

2.2

Ethyl 1-(4-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (02656-2)



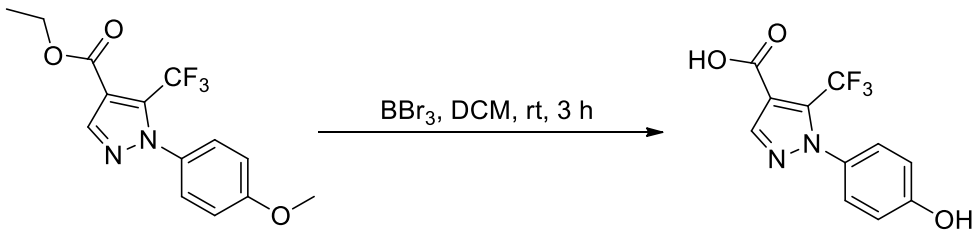
02656-1 **02656-2**

To a solution of (4-methoxyphenyl)hydrazine hydrochloride (1 g, 5.75 mmol) in EtOH (20 mL) was added ethyl (E)-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (2 g, 8.62 mmol), TEA (1.6 mL, 11.5 mmol), and HATU (564 mg, 1.49 mmol). The mixture was stirred at 80 °C for 2 hours. After the starting material was consumed, water (20 mL) was added, and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0~1/1, Silica gel, 40 g, 40 mL/min, UV 254) to afford the yellow oil product (783 mg, 43.4% yield).

ESI-MS *m/z* calcd for $[C_{14}H_{13}F_3N_2O_3]$ $[M+H]^+$: 315.1; found: 315.0

2.3

1-(4-Hydroxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (02656-3)



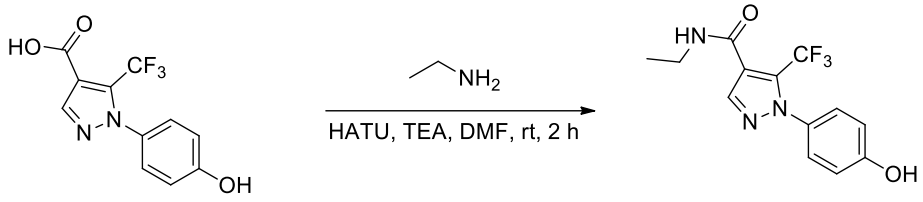
02656-2 **02656-3**

To a solution of ethyl 1-(4-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (400 mg, 1.27 mmol) in DCM (10 mL) was added BBr_3 (0.1 mL). The mixture was stirred at room temperature under nitrogen protection for 3 hours. After the starting material was consumed, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EA (30 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/2, Silica gel, 20 g, 20 mL/min, UV 254) to afford the white solid product (304 mg, 90.1% yield).

ESI-MS *m/z* calcd for $[C_{11}H_7F_3N_2O_3]$ $[M+H]^+$: 273.0; found: 273.0

2.4

N-Ethyl-1-(4-hydroxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide(02656-4)



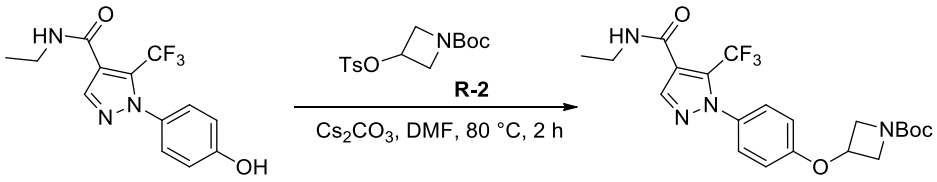
02656-3 02656-4

To a solution of 1-(4-hydroxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (200 mg, 0.76 mmol) in DMF (6 mL) was added HATU (433 mg, 1.16 mmol), ethylamine (0.4 mL, 0.92 mmol), and TEA (0.52 mL, 3.80 mmol). The mixture was stirred at room temperature for 2 hours. After the starting material was consumed, water (20 mL) was added, and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 20 g, 30 mL/min, UV 254) to afford the white solid product (94 mg, 41.4% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{12}F_3N_3O_2]$ $[M+H]^+$: 300.1; found:300.0

2.5

tert-Butyl3-(4-(4-(ethylaminocarbonyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenoxy)azetidin-1-carboxylate(02656-5)

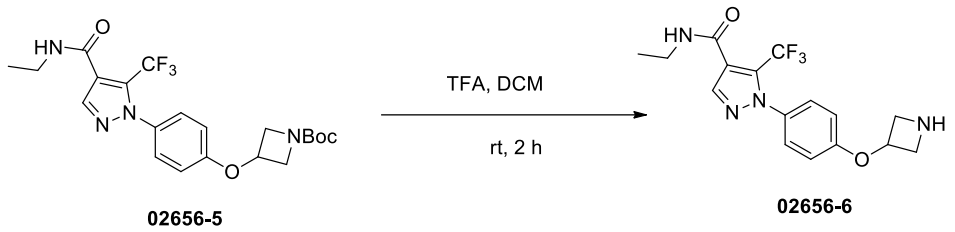


02656-4 02656-5

To a solution of N-ethyl-1-(4-hydroxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (50 mg, 0.17 mmol) in DMF (2 mL) was added tert-butyl 3-((4-methylphenyl)sulfonyloxy)azetidine-1-carboxylate (66 mg, 0.20 mmol), Cs_2CO_3 (111 mg, 0.34 mmol). The mixture was stirred at 80 °C for 2 hours. After the starting material was consumed, water (20 mL) was added, and the mixture was extracted with EA (30 mL) three times. The combined organic layers were washed with saturated saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 20 g, 30 mL/min, UV 254) to afford the white solid product (16 mg, 20.7% yield).

ESI-MS *m/z* calcd for $[C_{21}H_{25}F_3N_4O_4]$ $[M-56+H]^+$: 399.1; found: 399.0

2.61-(4-(Azetidin-3-yloxy)phenyl)-N-ethyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide(02656-6)



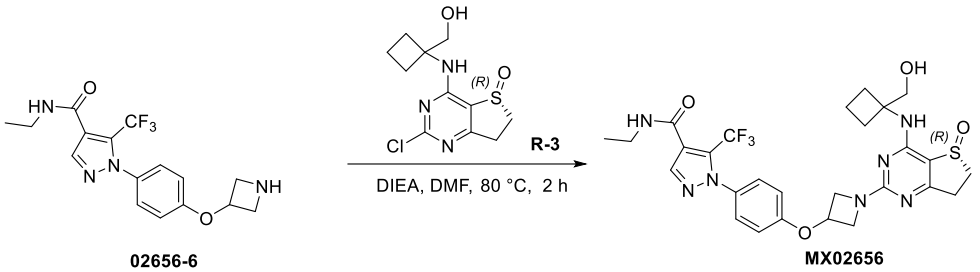
02656-5 02656-6

To a solution of tert-butyl 3-(4-(4-(ethylcarbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenoxy)azetidine-1-carboxylate (16 mg, 0.04 mmol) in DCM (2 mL) was added trifluoroacetic acid (0.2 mL). The mixture was stirred at room temperature for 2 hours. The mixture was concentrated, and the crude product was used directly in the next step.

ESI-MS *m/z* calcd for $[C_{16}H_{17}F_3N_4O_2]$ $[M+H]^+$:355.1; found:355.0

2.7

(R)-N-ethyl-1-(4-((1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)azetidin-3-yl)oxy)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (MX02656)



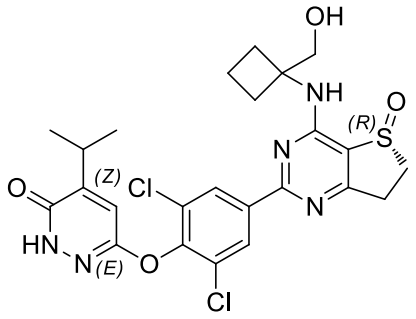
02656-6 MX02656

To a solution of 1-(4-(azetidin-3-yloxy)phenyl)-N-ethyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (10 mg, 0.03 mmol) in DMF (3 mL) was added (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (11 mg, 0.03 mmol) and DIEA (19 mg, 0.15 mmol). The mixture was stirred at 80 °C under nitrogen protection for 2 hours. After the starting material was consumed, the mixture was cooled, and water (10 mL) was added. The mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (6.56 mg, 36.1% yield).

ESI-MS *m/z* calcd for $[C_{27}H_{30}F_3N_7O_4S]$ $[M+H]^+$: 606.2; found: 605.9

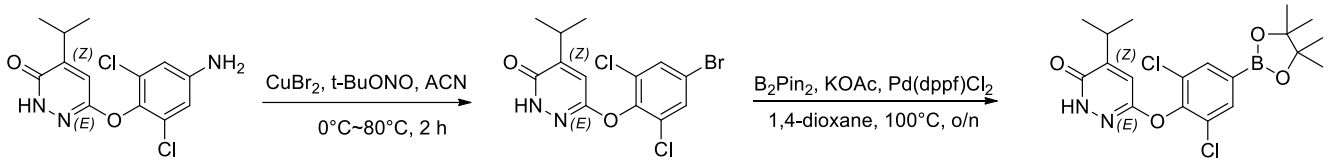
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (t, J = 5.2 Hz, 1H), 8.06 (s, 1H), 7.45– 7.43(m, 3H), 7.07– 7.03 (m, 2H), 5.23– 5.19 (m, 1H),4.84 (t, J = 5.6 Hz, 1H), 4.52– 4.48 (m, 2H),

3.98– 3.96 (m, 2H), 3.74 – 3.69 (m, 2H), 3.46 – 3.44 (m, 1H), 3.28 – 3.14 (m, 3H), 2.98 – 2.84 (m, 2H), 2.39 – 2.56 (m, 2H), 2.16 – 2.11 (m, 2H), 1.83 – 1.64 (m, 2H), 1.11 (t, *J* = 7.2 Hz,3H).

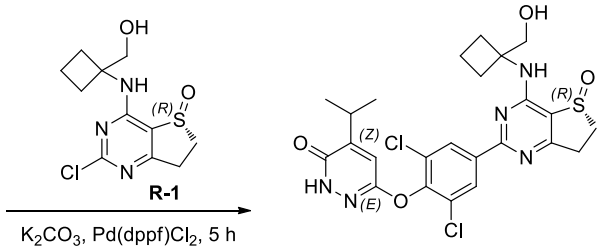


MX02660

1. Synthetic scheme:



02660-0 **02660-1** **02660-2**

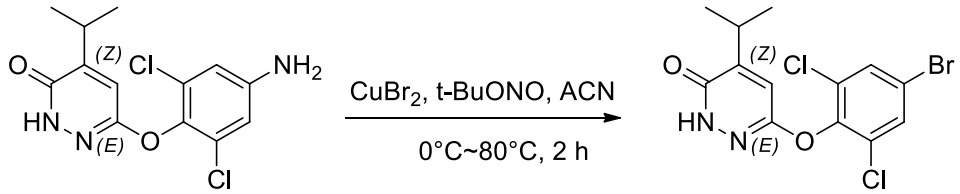


MX02660

2. Experimental section:

2.1

6-(4-bromo-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one (02660-1)



02660-0 **02660-1**

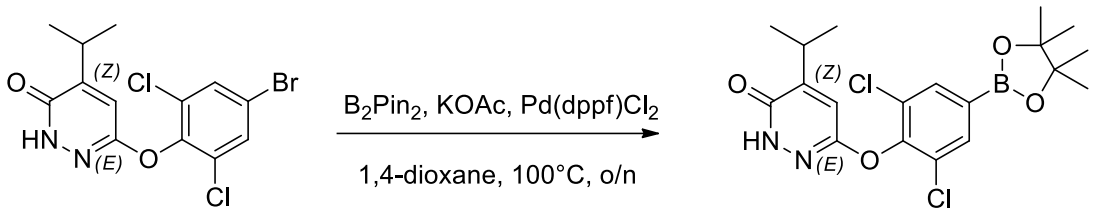
To a solution of 6-(4-amino-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one (314.2 mg, 1.0 mmol) in HBr (10.0 mL, 40% v/v aqueous solution) was added aqueous $NaNO_2$ (69.0 mg, 1.0 mmol) in 0.5 mL H_2O at 0 °C. The mixture was stirred at 0 °C under argon

protection for 0.5 hours. Then, $CuBr_2$ (223.5 mg, 1.0 mmol) was added, and the mixture was stirred at 80 °C for 2 hours. The reaction was quenched with water (20 mL) and extracted with DCM (20 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 20 g, 30 mL/min, UV 254) to afford the yellow oil product (340.0 mg, 68.0% yield).

ESI-MS *m/z* calcd for $[C_{13}H_{11}BrCl_2N_2O_2]$ $[M+H]^+$:376.9; found:377.2.

2.2

6-(2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-4-isopropylpyridazin-3(2H)-one (02660-2)



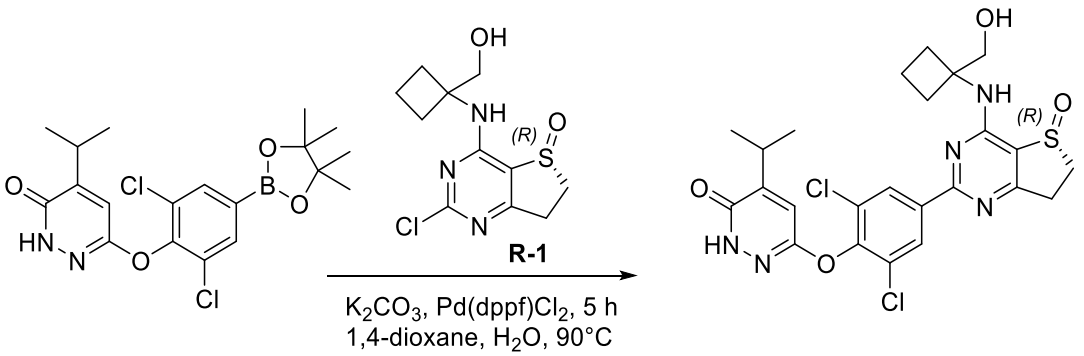
02660-1 **02660-2**

To a solution of 6-(4-bromo-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one (340.0 mg, 0.9 mmol) in 1,4-dioxane (15.0 mL) was added B_2Pin_2 (1143.0 mg, 4.5 mmol), KOAc (441.0 mg, 4.5 mmol), and $Pd(dppf)Cl_2$ (66.0 mg, 0.09 mmol). The mixture was stirred at 100 °C under nitrogen protection overnight. After the starting material was consumed, the mixture was cooled and concentrated under reduced pressure. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 40 g, 40 mL/min, UV 254) to afford the brown solid product (46.0 mg, 12.0% yield).

ESI-MS *m/z* calcd for $[C_{19}H_{23}BCl_2N_2O_4]$ $[M+H]^+$:425.2; found:425.3

2.3

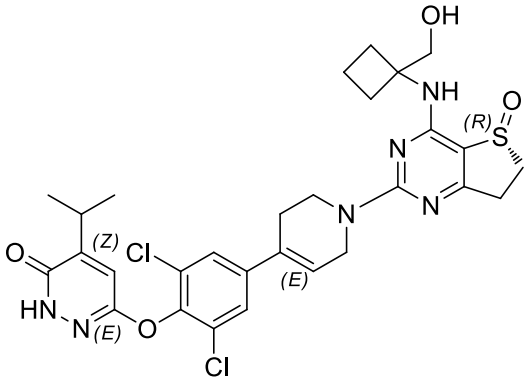
(R)-6-(2,6-dichloro-4-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)phenoxy)-4-isopropylpyridazin-3(2H)-one (MX02660)



To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (28.0 mg, 0.1 mmol) in 1,4-dioxane/H_2O (2.5 mL, v/v=4/1) was added 6-(2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-4-isopropylpyridazin-3(2H)-one (45.0 mg, 0.1 mmol), K_2CO_3 (28.0 mg, 0.2 mmol), and $Pd(dppf)Cl_2$ (15.0 mg, 0.02 mmol). The mixture was stirred at 90 °C under nitrogen protection for 5 hours. After the starting material was consumed, water (10 mL) was added, and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (15.0 mg, 27.3% yield).

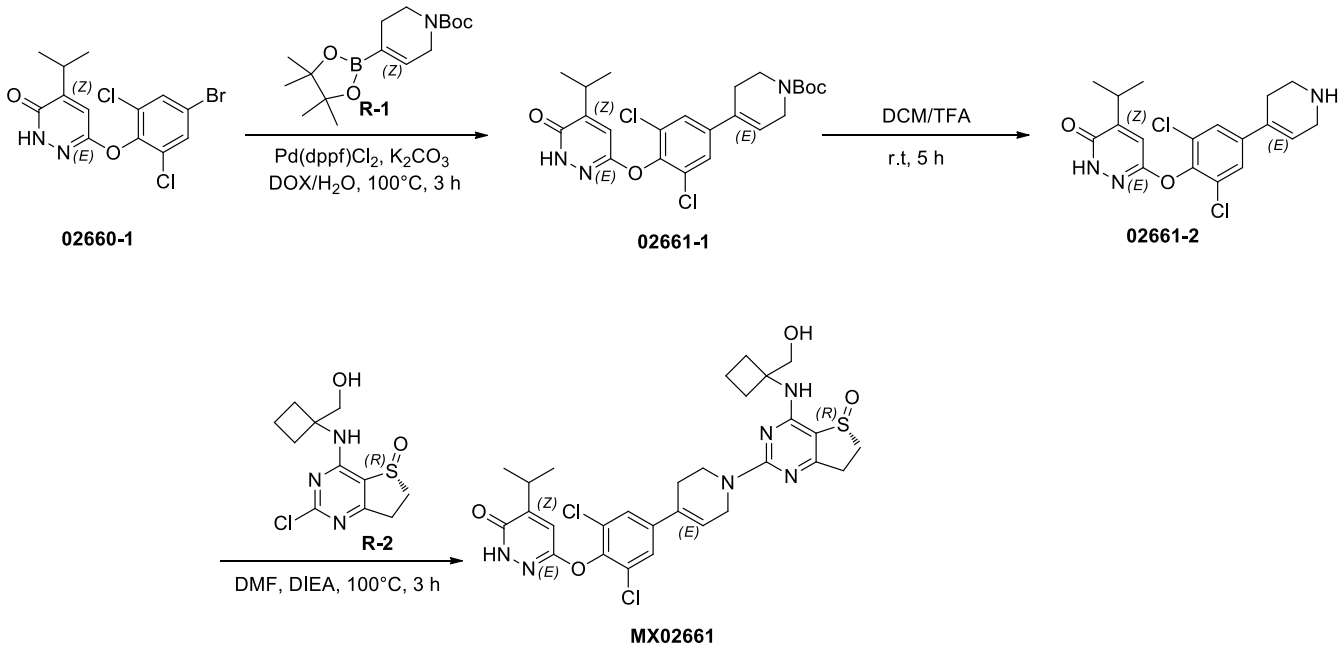
ESI-MS *m/z* calcd for $[C_{24}H_{25}Cl_2N_5O_4S]$ $[M+H]^+$: 550.1; found: 550.2

^1H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.35 (s, 2H)，8.27 (s, 1H)，7.44 (s, 1H)，4.96(t, J = 6.0 Hz, 1H), 3.82 – 3.78 (m, 2H), 3.70 – 3.62 (m, 2H), 3.42 –3.35 (m, 1H), 3.09 – 3.02 (m, 2H), 2.47 –2.35 (m, 2H), 2.33 –2.26 (m, 2H), 1.89 –1.81 (m, 2H)，1.20 (d, J = 6.8 Hz, 6H).



MX02661

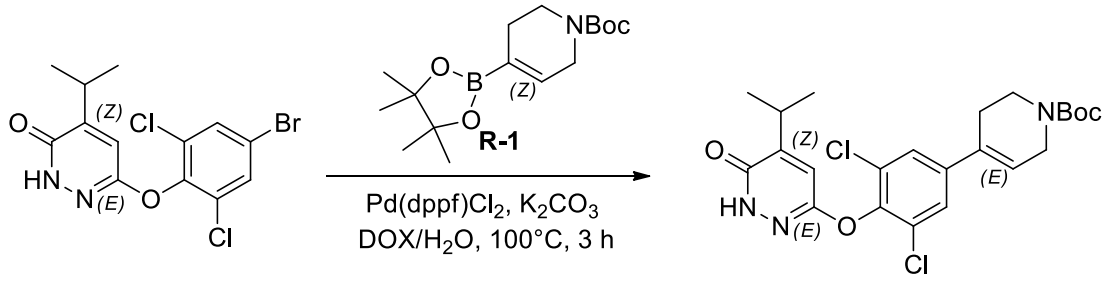
1. Synthetic scheme:



2. Experimental section:

2.1

tert-Butyl4-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (02661-1)

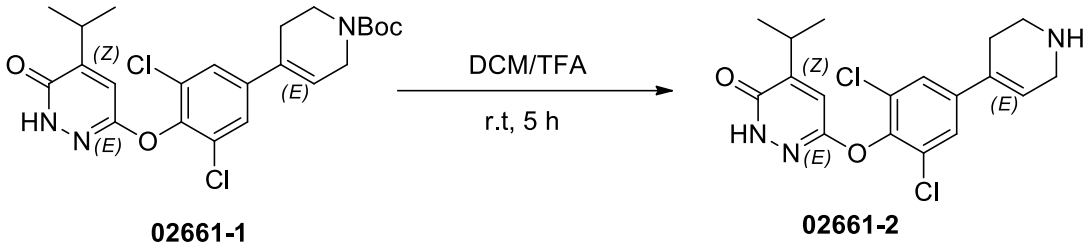


To a solution of 6-(4-bromo-2,6-dichlorophenoxy)-4-isopropylpyridazin-3(2H)-one (113.4 mg, 0.3 mmol) in 1,4-dioxane (5 mL) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (111.3 mg, 0.36 mmol), K_2CO_3 (83.0 mg, 0.6 mmol), and $Pd(dppf)Cl_2$ (44.0 mg, 0.06 mmol). The mixture was stirred at 100 °C under nitrogen protection for 3 hours. After the starting material was consumed, water (10 mL) was added, and the mixture was extracted with EA (10 mL) three times. The combined organic layers were washed with saturated saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (EA/PE = 0/1~1/1, Silica gel, 20 g, 40 mL/min, UV 254) to afford the brown solid product (60.0 mg, 41.8% yield).

ESI-MS *m/z* calcd for $[C_{23}H_27Cl_2N_3O_4]$ $[M+H]^+$:480.1; found:479.9.

2.2

6-(2,6-Dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-4-isopropylpyridazin-3(2H)-one (02661-2)



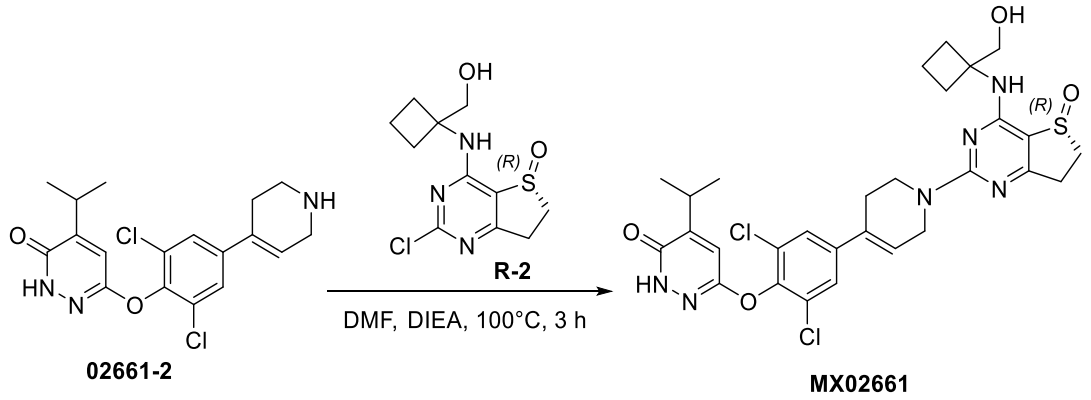
02661-1 02661-2

To a solution of tert-butyl 4-(3,5-dichloro-4-((5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (60.0 mg, 0.125 mmol) in DCM (5.0 mL) was added TFA (0.5 mL). The mixture was stirred under nitrogen protection for 5 hours. After the starting material was consumed, the mixture was cooled and concentrated under reduced pressure to afford the brown solid product (50.0 mg, 100.0% yield).

ESI-MS *m/z* calcd for $[C_{18}H_{19}Cl_2N_3O_2]$ $[M+H]^+$:380.1; found:379.9

2.3

(R)-6-(2,6-Dichloro-4-(1-(4-((1-(hydroxymethyl)cyclobutyl)amino)-5-oxido-6,7-dihydrothieno[3,2-d]pyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)-4-isopropylpyridazin-3(2H)-one (MX02661)



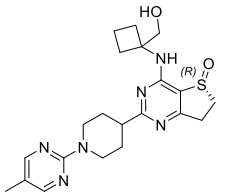
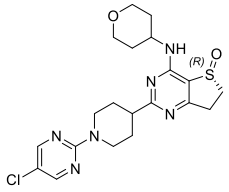
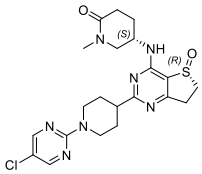
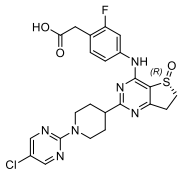
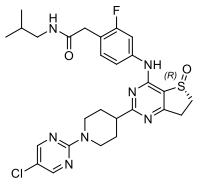
To a solution of (R)-2-chloro-4-((1-(hydroxymethyl)cyclobutyl)amino)-6,7-dihydrothieno[3,2-d]pyrimidine 5-oxide (37.4 mg, 0.13 mmol) in DMF (5 mL) was added 6-(2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-4-isopropylpyridazin-3(2H)-one (50.0 mg, 0.13 mmol) and DIEA (1.0 mL). The mixture was stirred at 100 °C for 3 hours. After completion, the mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC (MeCN/H_2O (10 mmol/L NH_4HCO_3), X-Select 10 μm 19*250 mm, 20 mL/min, UV 254) to afford the white solid product (35.0 mg, 42.7% yield).

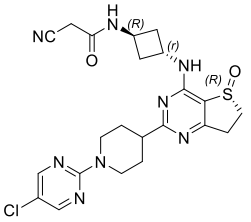
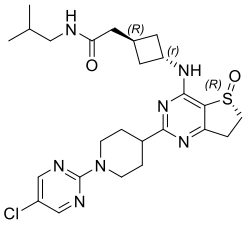
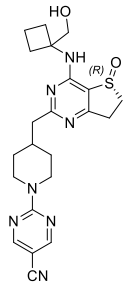
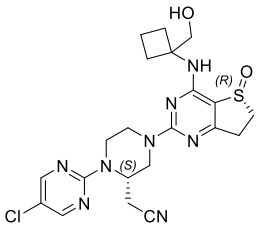
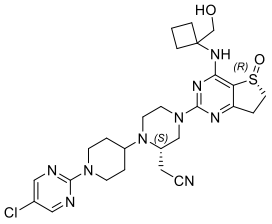
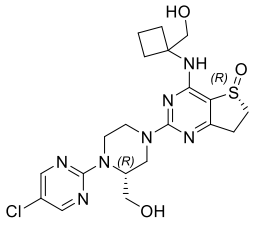
ESI-MS *m/z* calcd for $[C_{29}H_{32}Cl_2N_6O_4S]$ $[M+H]^+$: 631.2; found: 631.2

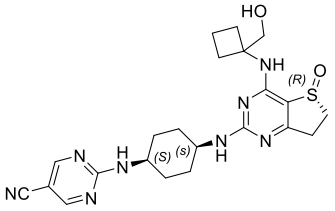
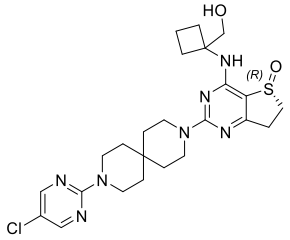
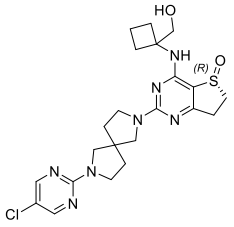
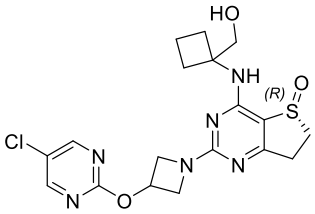
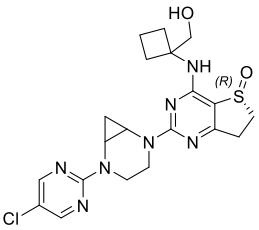
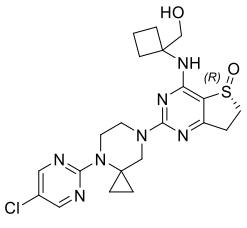
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 7.66 (s, 2H)， 7.39(d, J = 3.6 Hz, 2H),6.44 (s, 1H)， 4.85(t, J = 5.6 Hz, 1H), 4.40 – 4.32 (m, 2H), 3.97(t, J = 5.2 Hz, 2H), 3.79 – 3.71 (m, 2H), 3.47 –3.39 (m, 1H), 3.28 –3.18 (m, 1H), 3.07 –3.02 (m, 1H), 3.00 –2.92 (m, 1H), 2.90 –2.84 (m, 1H), 2.53 –2.50 (m, 2H), 2.45 –2.30 (m, 2H), 2.22 –2.17 (m, 2H), 1.83 – 1.73 (m, 2H)， 1.19 (d, J = 6.8 Hz, 6H).

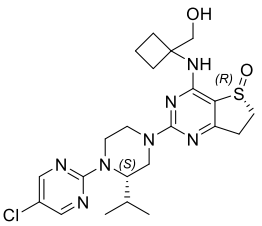
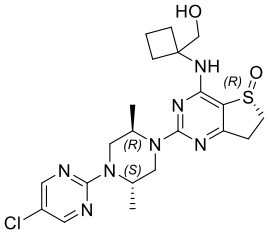
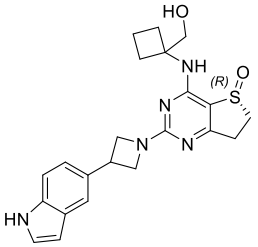
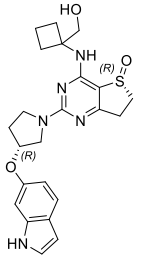
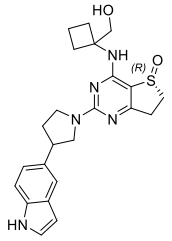
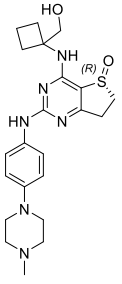
The compounds prepared by using the above methods or by referring to the above methods and mass spectrometry data thereof are summarized in Table 1 below:

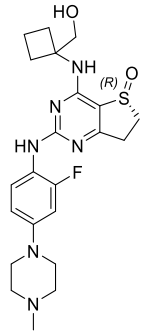
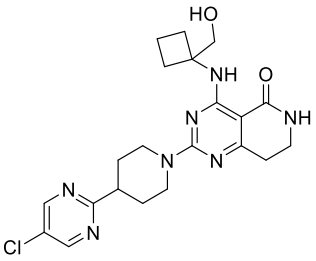
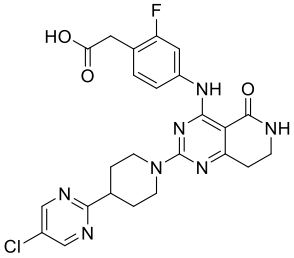
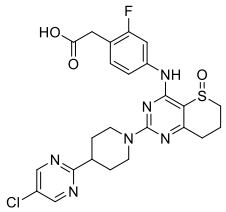
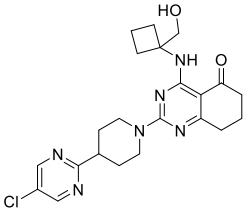
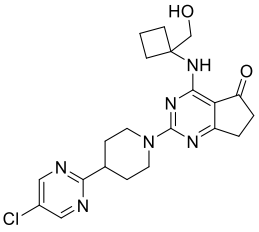
Table 1: Example compounds (the prefix "MX02" is omitted in the numbering)

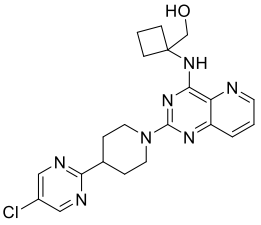
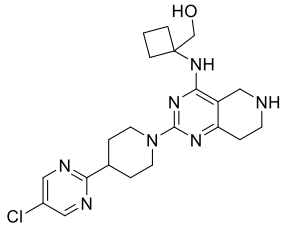
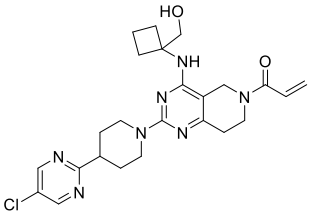
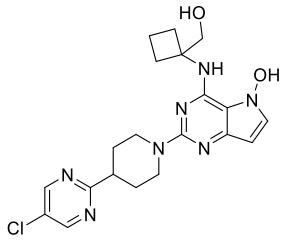
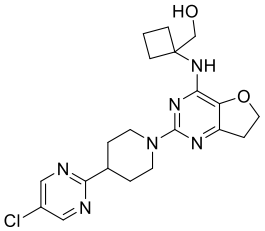
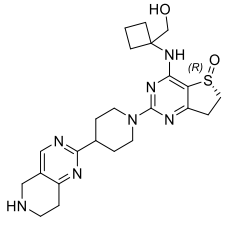
No.	Chemical structure	$[M+H]^+$
002		429.2
003		449.2
004		476.2
005		517.2
006		572.2

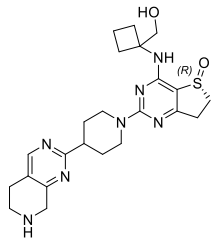
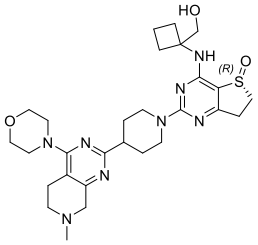
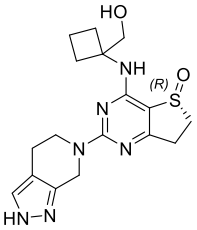
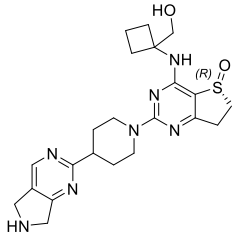
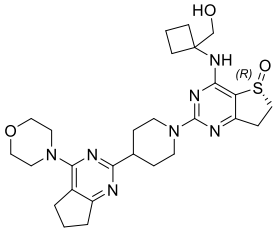
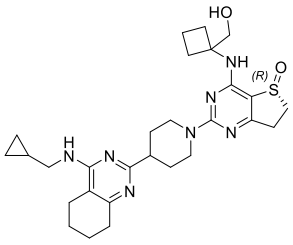
No.	Chemical structure	$[M+H]^+$
007		501.2
008		532.2
009		454.2
010		489.2
011		572.3
012		480.1

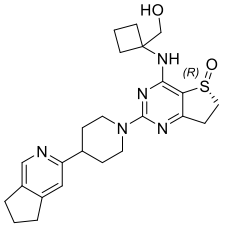
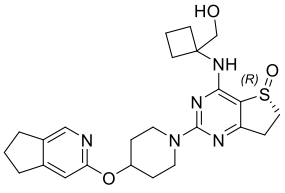
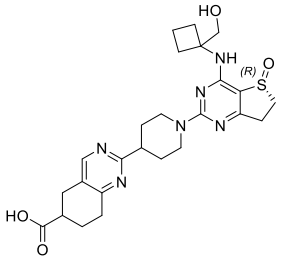
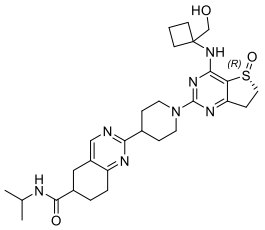
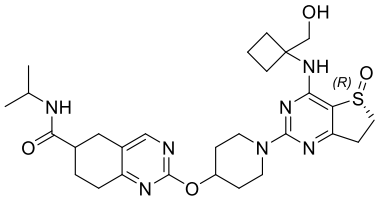
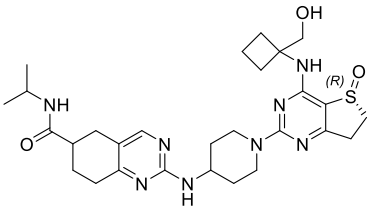
No.	Chemical structure	$[M+H]^+$
013		469.3
014		518.2
017		490.2
019		437.2
020		462.2
021		476.2

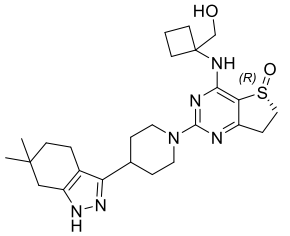
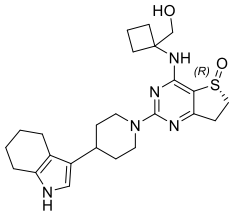
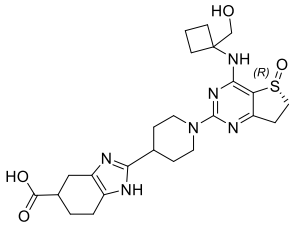
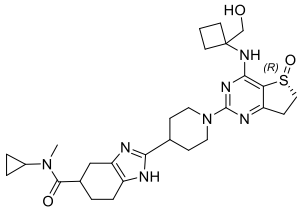
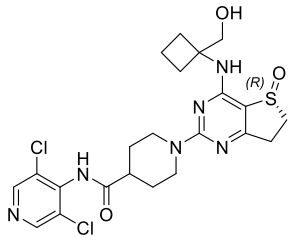
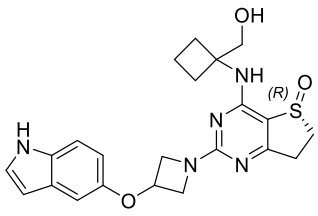
No.	Chemical structure	$[M+H]^+$
022		492.2
023		478.2
024		424.2
025		454.2
026		438.2
027		443.2

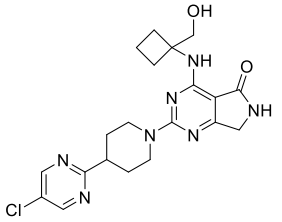
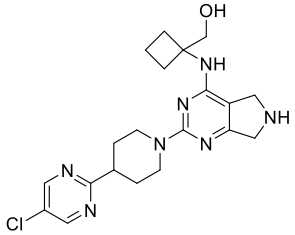
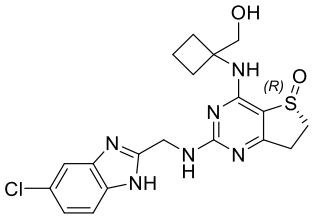
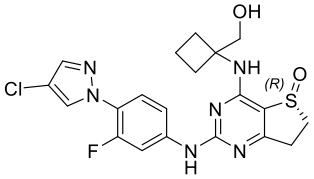
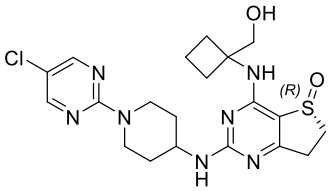
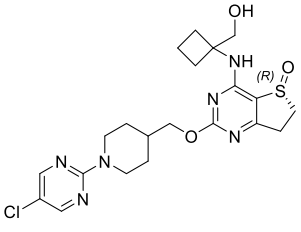
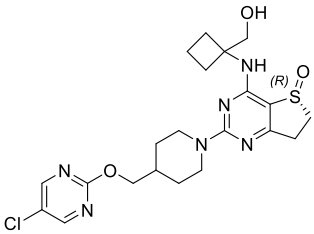
No.	Chemical structure	$[M+H]^+$
028		461.2
029		442.2
030		512.2
032		531.2
033		443.2
034		429.2

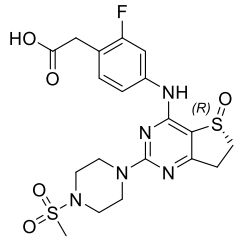
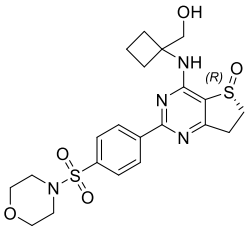
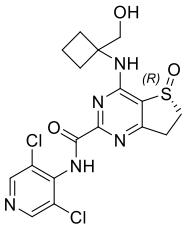
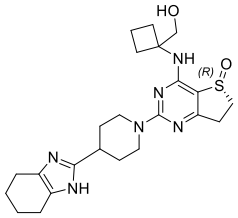
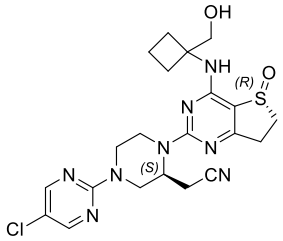
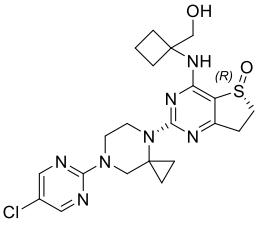
No.	Chemical structure	$[M+H]^+$
035		426.2
036		430.2
037		484.2
038		430.2
039		417.2
040		470.2

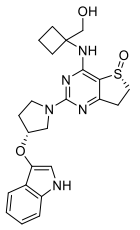
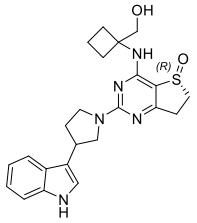
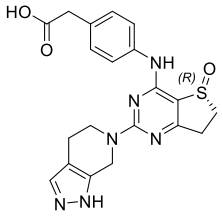
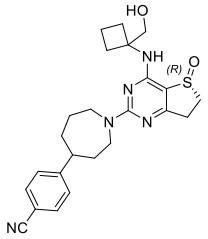
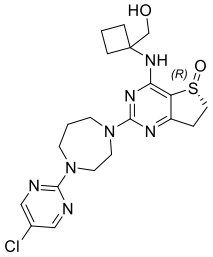
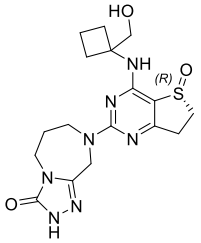
No.	Chemical structure	$[M+H]^+$
041		470.3
042		569.3
043		375.2
044		456.2
045		540.3
046		538.3

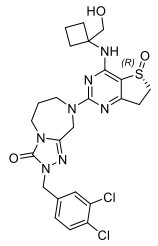
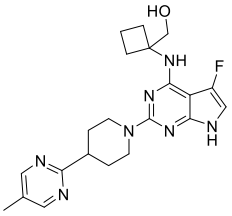
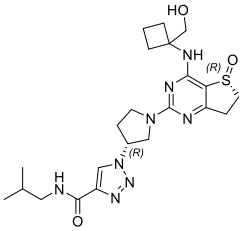
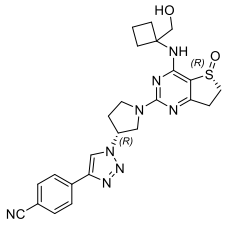
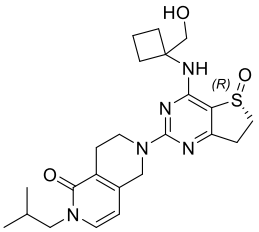
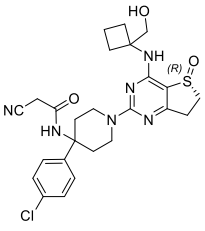
No.	Chemical structure	$[M+H]^+$
047		454.3
048		470.3
049		513.3
050		554.3
051		570.3
052		569.2

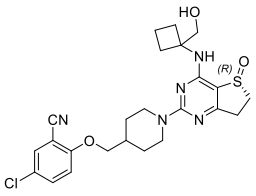
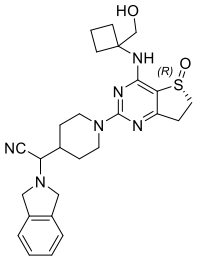
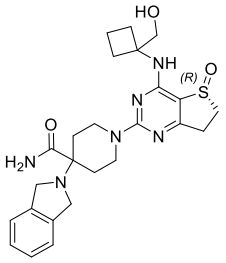
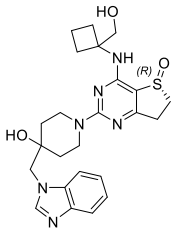
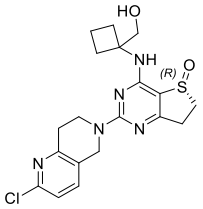
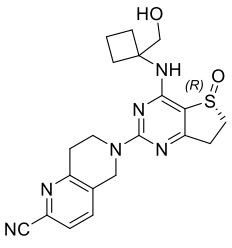
No.	Chemical structure	$[M+H]^+$
053		485.3
054		456.3
055		501.2
056		554.3
057		525.1
058		440.3

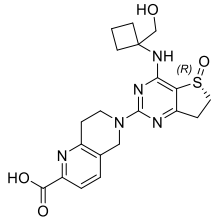
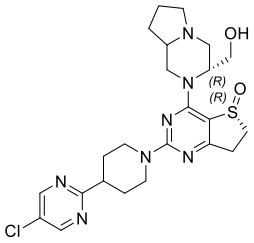
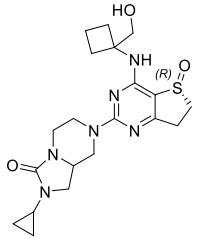
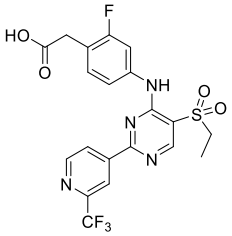
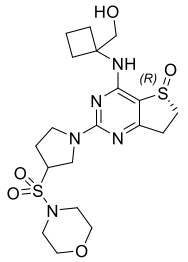
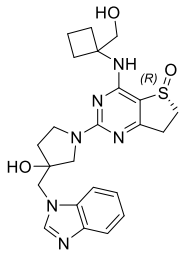
No.	Chemical structure	$[M+H]^+$
059		430.3
060		416.3
061		433.2
062		463.2
063		464.2
064		479.2
065		479.2

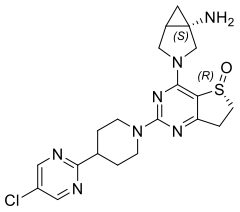
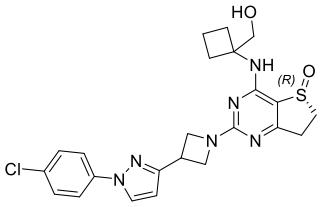
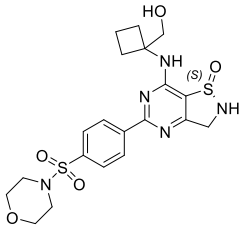
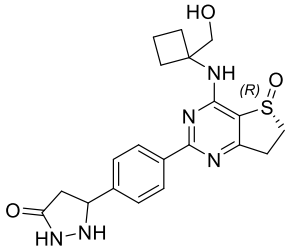
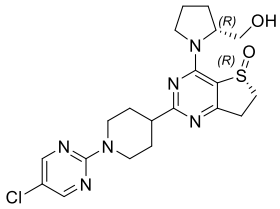
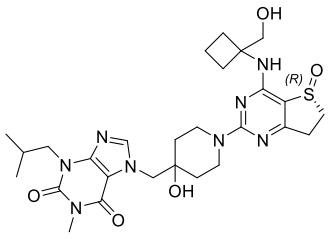
No.	Chemical structure	$[M+H]^+$
066		484.2
067		479.2
068		442.2
069		457.2
071		489.2
072		476.2

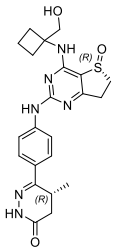
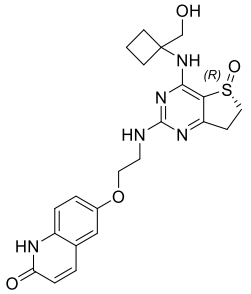
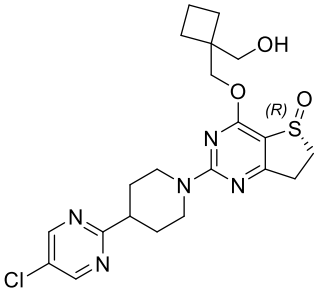
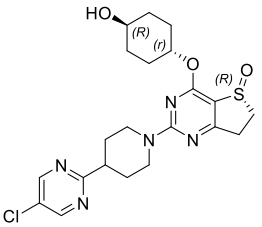
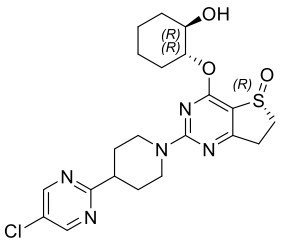
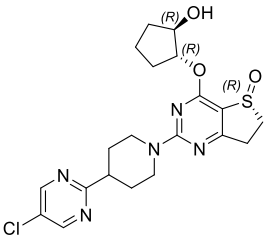
No.	Chemical structure	$[M+H]^+$
073		454.2
074		438.2
075		425.2
076		452.2
077		464.2
078		406.2

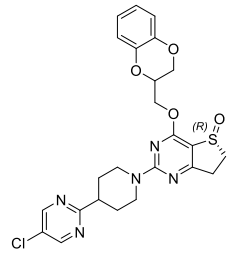
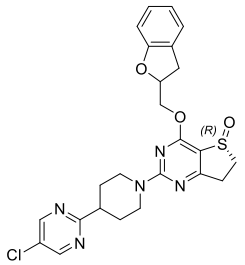
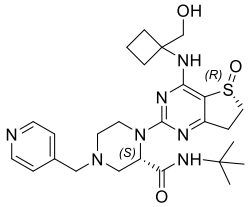
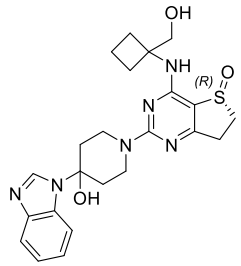
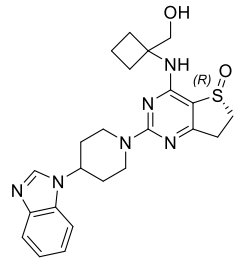
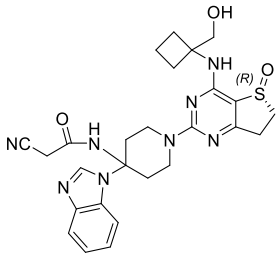
No.	Chemical structure	$[M+H]^+$
079		564.2
080		412.2
081		489.2
082		491.2
083		458.2
084		529.2

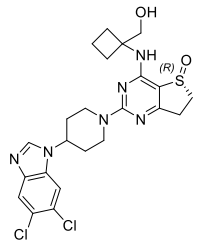
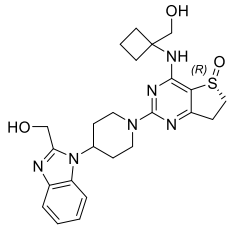
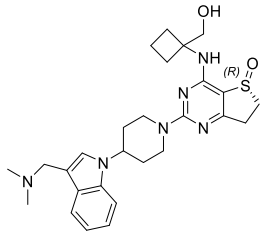
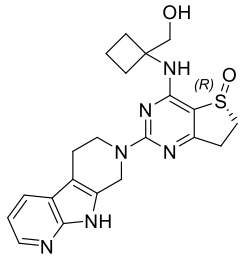
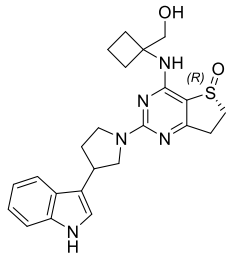
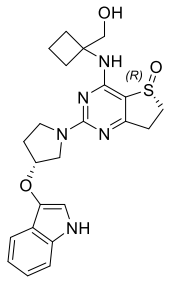
No.	Chemical structure	$[M+H]^+$
085		502.2
086		493.2
087		497.2
088		483.2
089		420.2
090		411.2

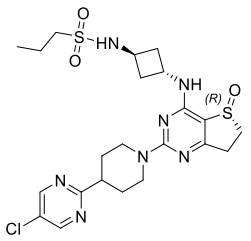
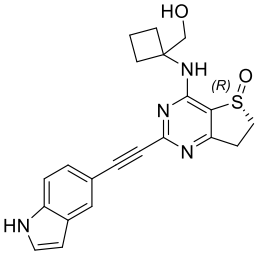
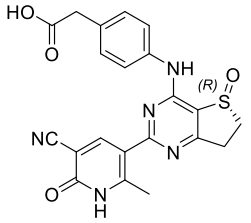
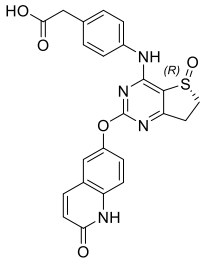
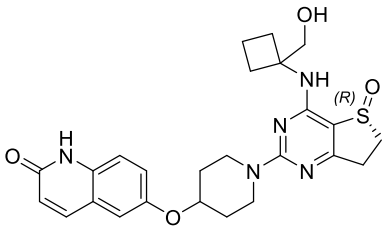
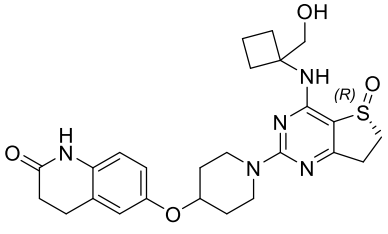
No.	Chemical structure	$[M+H]^+$
091		430.2
092		504.2
093		433.2
094		485.2
095		472.2
096		469.2

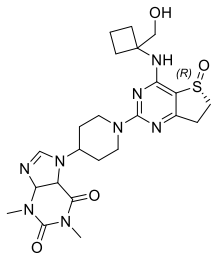
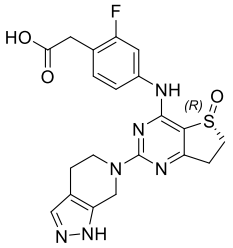
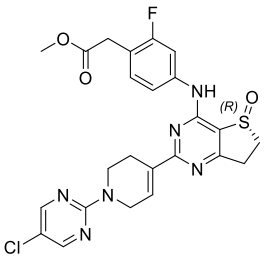
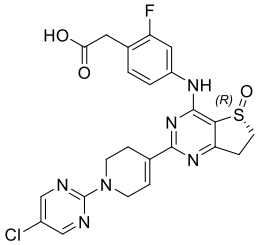
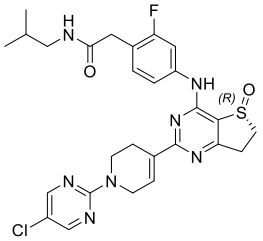
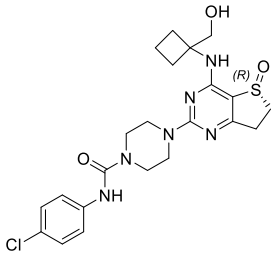
No.	Chemical structure	$[M+H]^+$
097		446.2
098		485.2
099		480.2
100		414.2
101		449.2
102		587.2

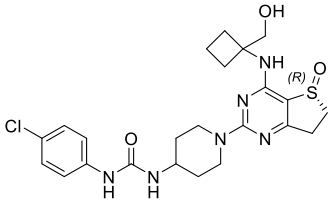
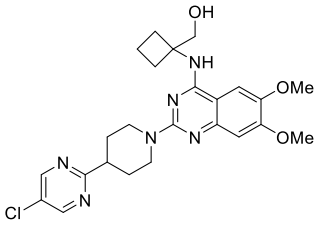
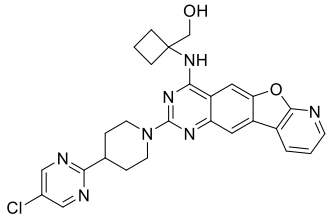
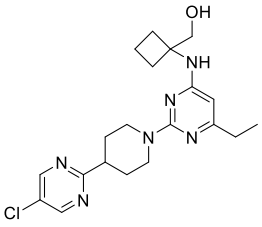
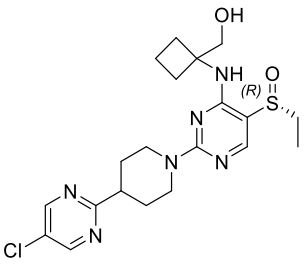
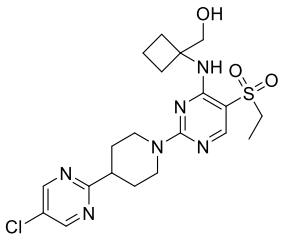
No.	Chemical structure	$[M+H]^+$
103		455.2
104		456.2
105		464.2
106		464.2
107		464.2
108		450.2

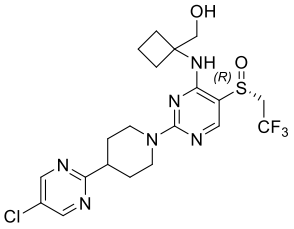
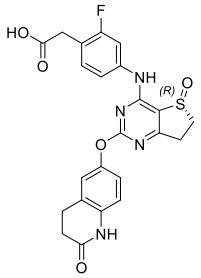
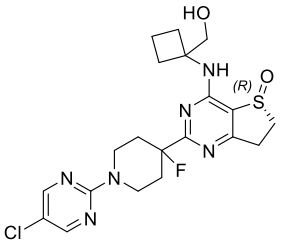
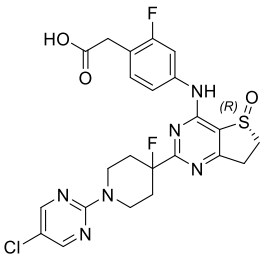
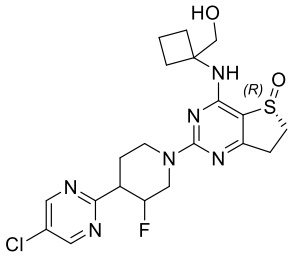
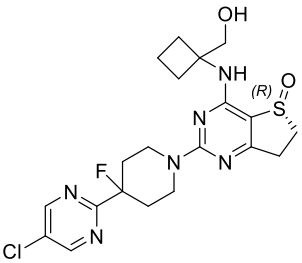
No.	Chemical structure	$[M+H]^+$
109		514.2
110		498.2
111		528.2
112		469.2
113		453.2
114		535.2

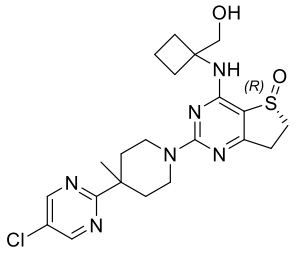
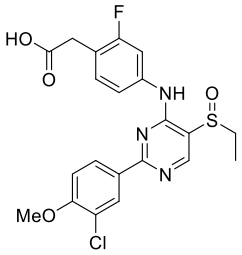
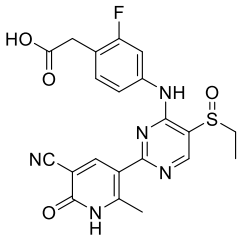
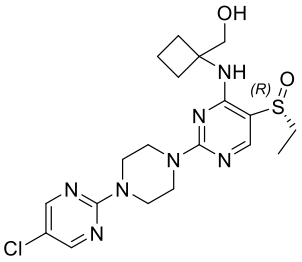
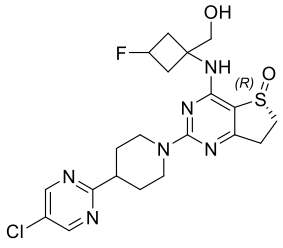
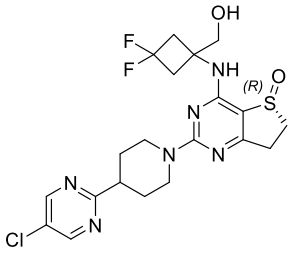
No.	Chemical structure	$[M+H]^+$
115		521.2
116		483.2
117		509.2
118		425.2
119		438.2
120		454.2

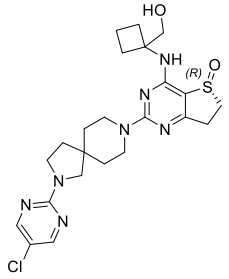
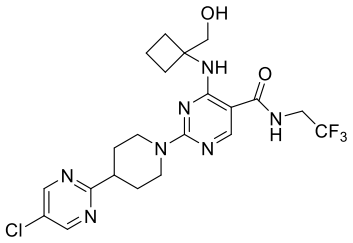
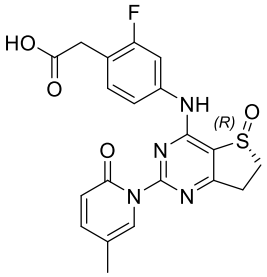
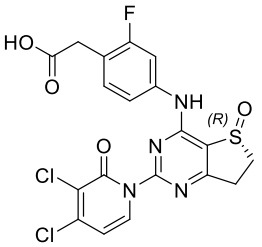
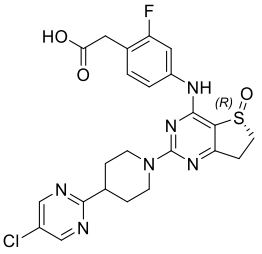
No.	Chemical structure	$[M+H]^+$
121		540.2
122		393.2
123		436.2
124		463.2
125		496.2
126		498.2

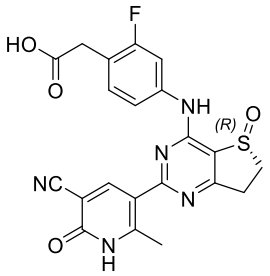
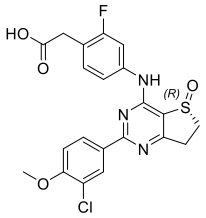
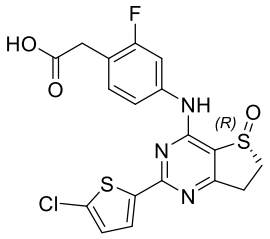
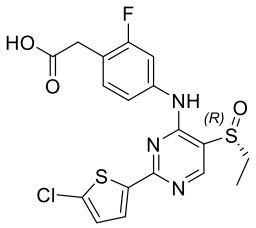
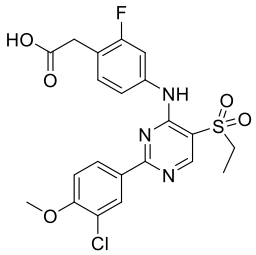
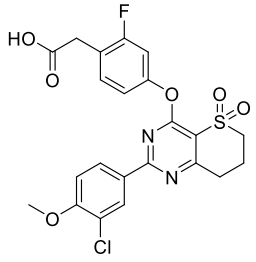
No.	Chemical structure	$[M+H]^+$
127		517.2
128		443.2
129		529.2
130		515.2
131		570.2
132		491.2

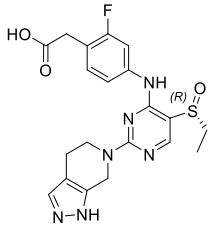
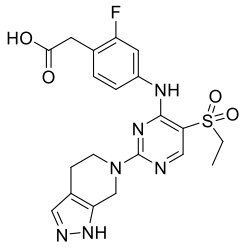
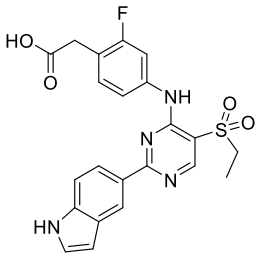
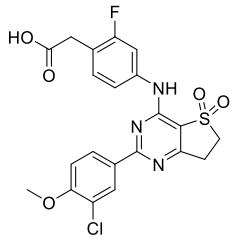
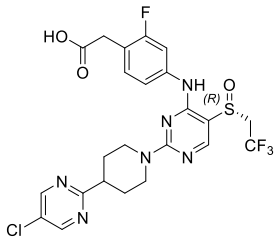
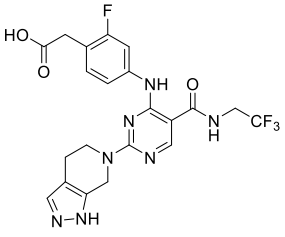
No.	Chemical structure	$[M+H]^+$
133		505.2
134		485.2
135		516.2
136		403.2
137		451.2
138		467.2

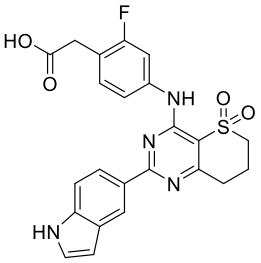
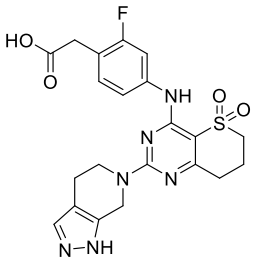
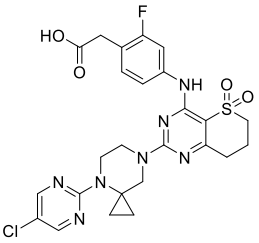
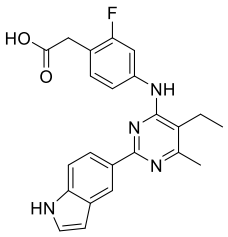
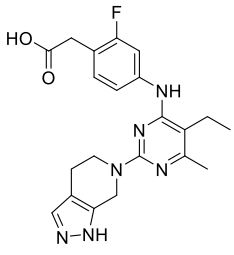
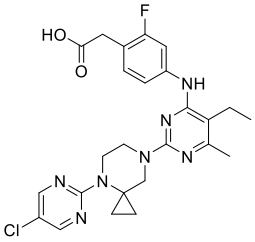
No.	Chemical structure	$[M+H]^+$
139		505.2
140		483.2
141		467.2
142		535.2
143		467.2
145		467.2

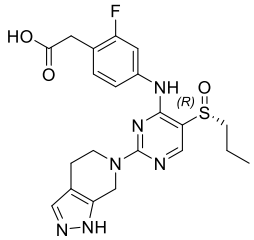
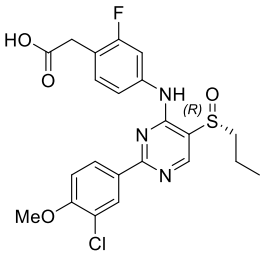
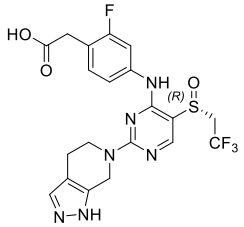
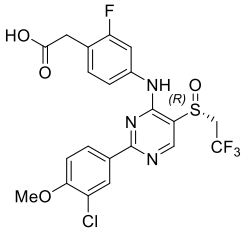
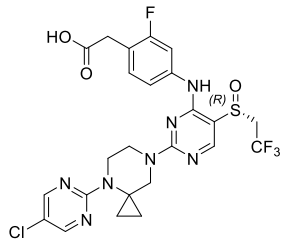
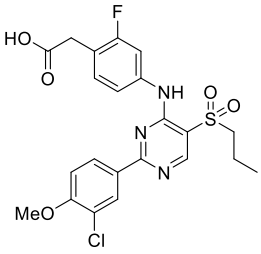
No.	Chemical structure	$[M+H]^+$
146		463.2
147rac		464.2
148rac		456.2
149		452.2
150		467.2
151		485.2

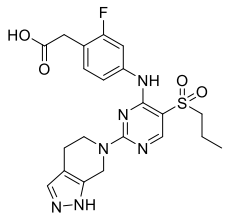
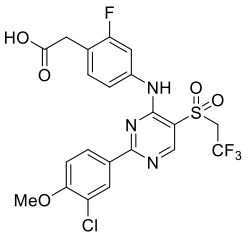
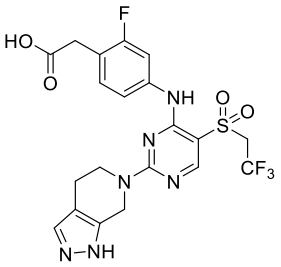
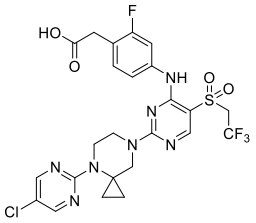
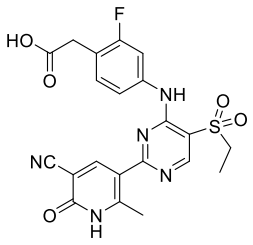
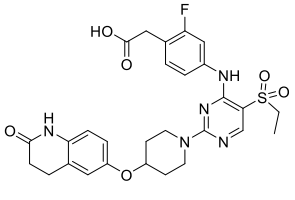
No.	Chemical structure	$[M+H]^+$
152		504.2
153		500.2
154		429.2
155		483.2
156		517.2

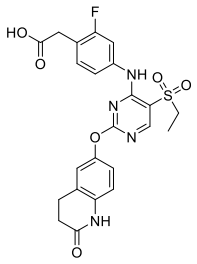
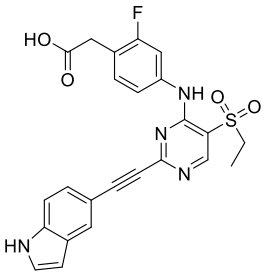
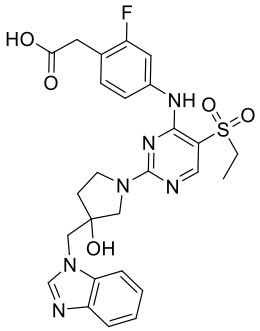
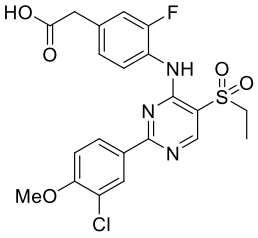
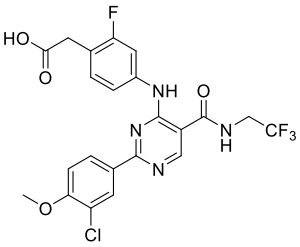
No.	Chemical structure	$[M+H]^+$
157		454.2
158		462.2
159		438.2
160		440.2
161		480.2
162		493.2

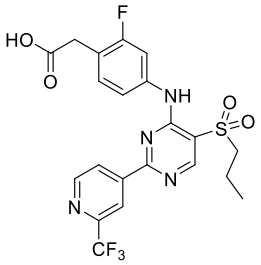
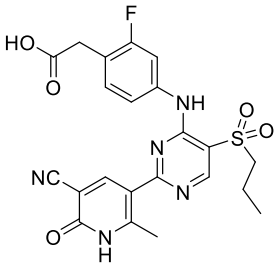
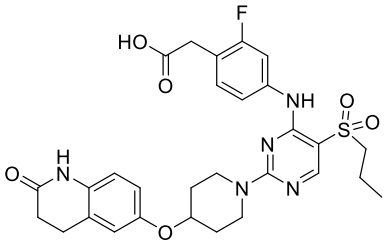
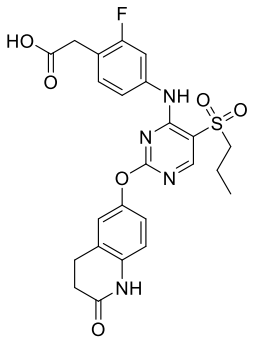
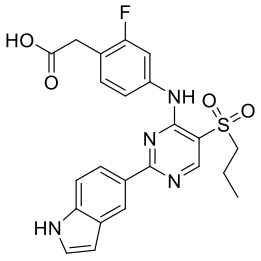
No.	Chemical structure	$[M+H]^+$
163		445.2
164		461.2
165		455.2
166		478.2
167		573.2
168		494.2

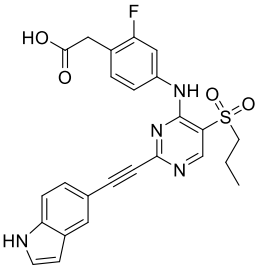
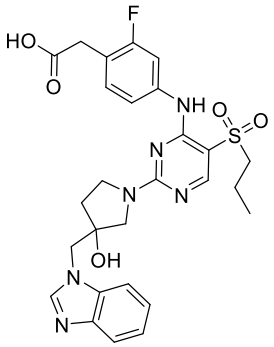
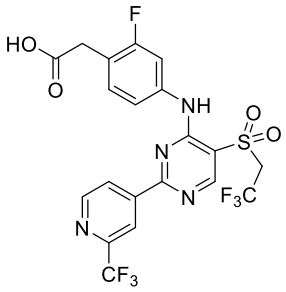
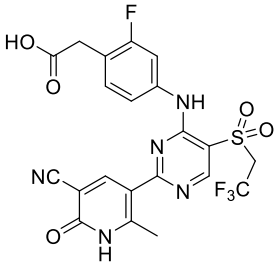
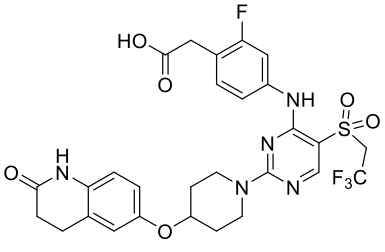
No.	Chemical structure	$[M+H]^+$
169		467.2
170		473.2
171		574.2
172		405.2
173		411.2
174		512.2

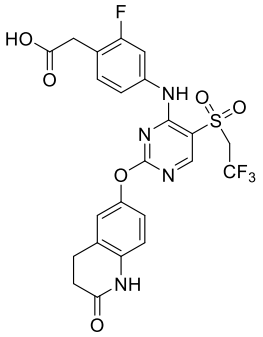
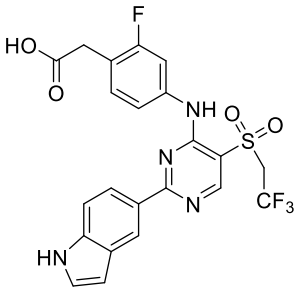
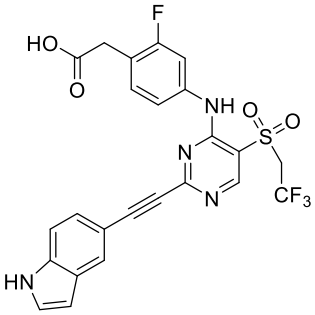
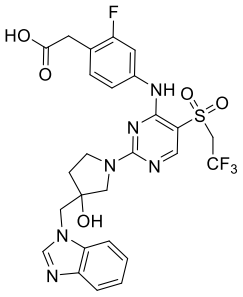
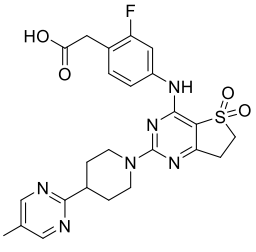
No.	Chemical structure	$[M+H]^+$
175		459.2
176		478.2
177		499.2
178		518.2
179		600.2
180		494.2

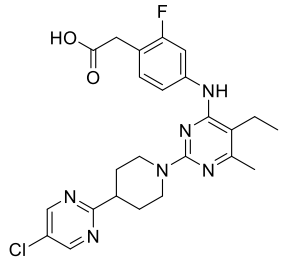
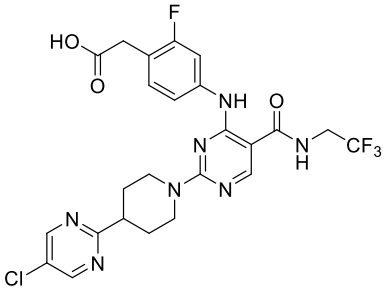
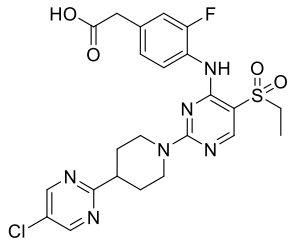
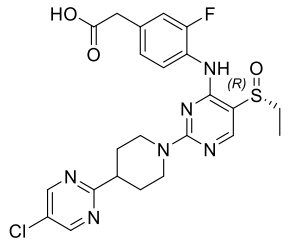
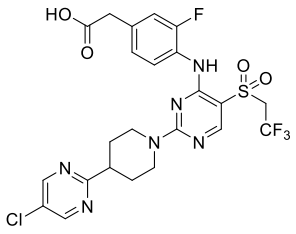
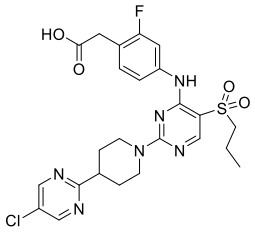
No.	Chemical structure	$[M+H]^+$
181		475.2
182		534.2
183		515.2
184		616.2
185		472.2
186		584.2

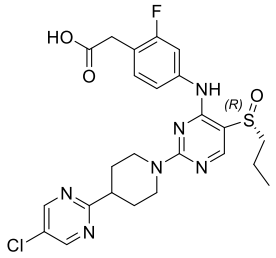
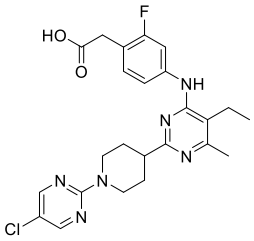
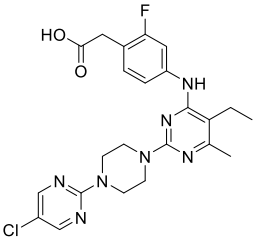
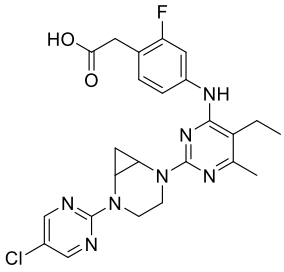
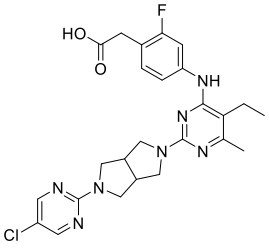
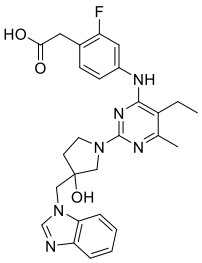
No.	Chemical structure	$[M+H]^+$
187		501.2
188		479.2
189		555.2
190		480.2
191		513.2

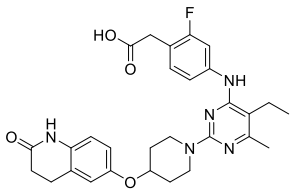
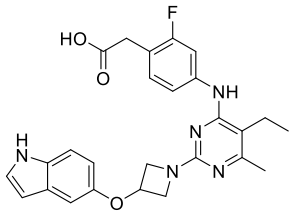
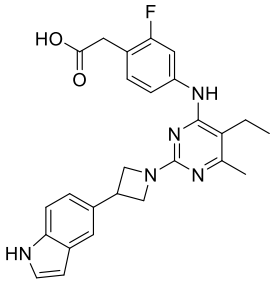
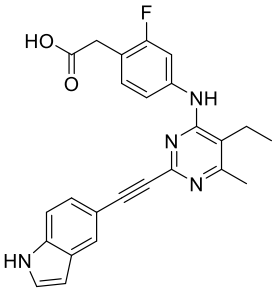
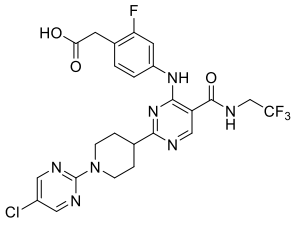
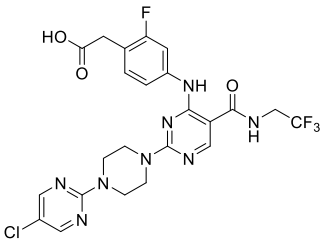
No.	Chemical structure	$[M+H]^+$
192		499.2
193		486.2
194		598.2
195		515.2
196		469.2

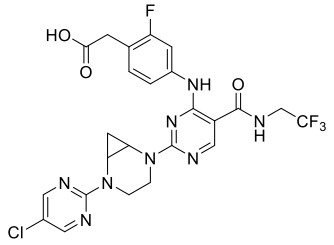
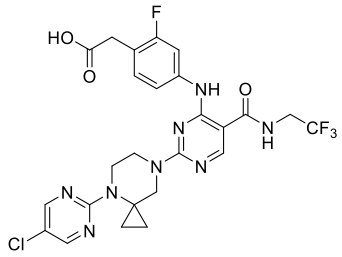
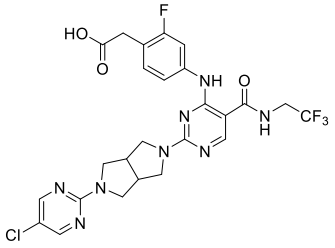
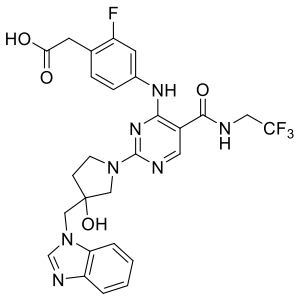
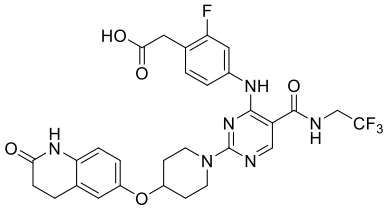
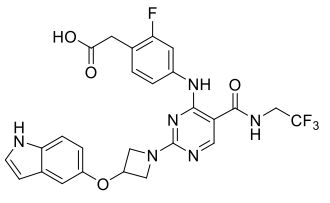
No.	Chemical structure	$[M+H]^+$
197		493.2
198		569.2
199		539.2
200		526.2
201		638.2

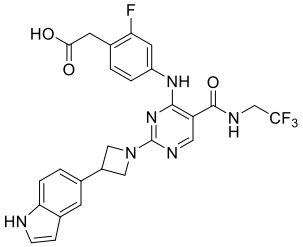
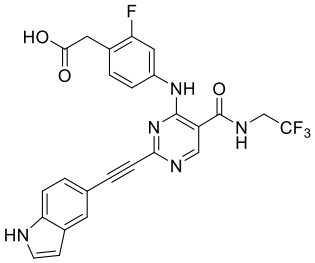
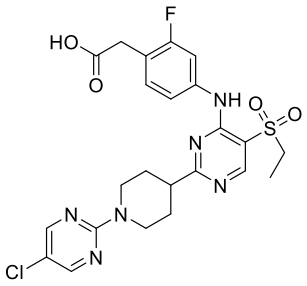
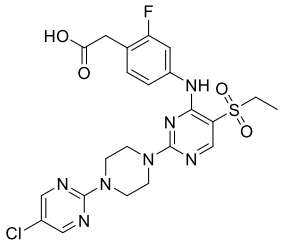
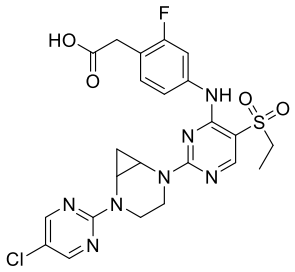
No.	Chemical structure	$[M+H]^+$
202		555.2
203		509.2
204		533.2
205		609.2
206		533.2

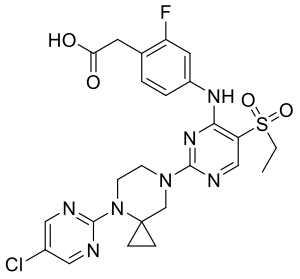
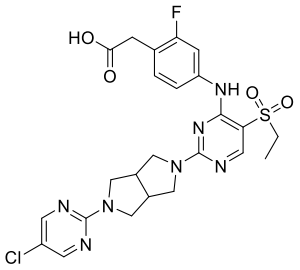
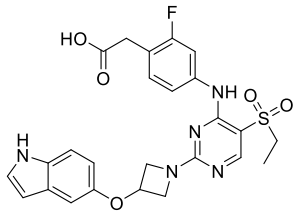
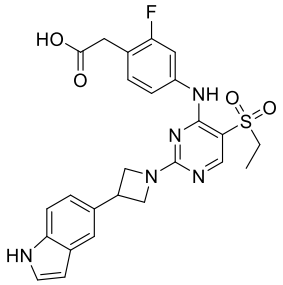
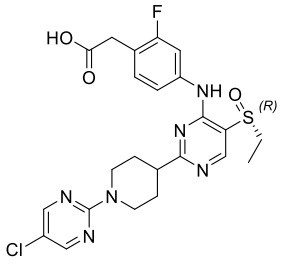
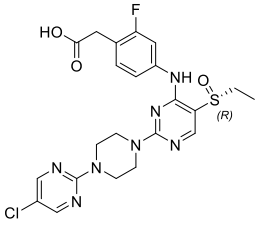
No.	Chemical structure	$[M+H]^+$
207		485.2
208		568.2
209		535.2
210		519.2
211		589.2
212		549.2

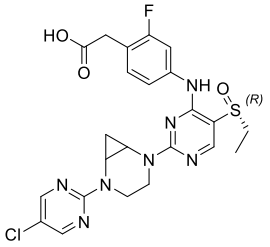
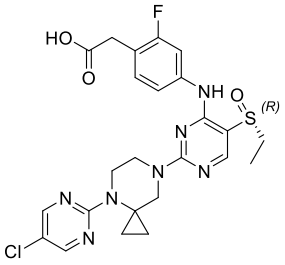
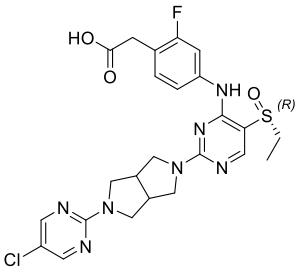
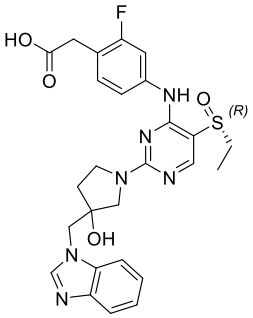
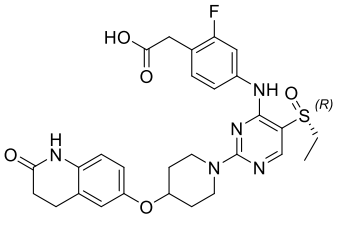
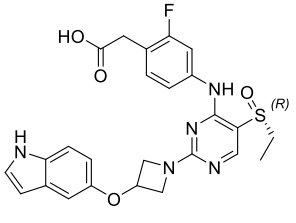
No.	Chemical structure	$[M+H]^+$
213		533.2
214		485.2
215		486.2
216		498.2
217		512.2
218		505.2

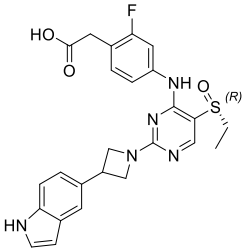
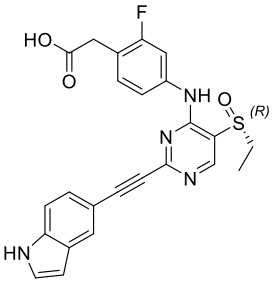
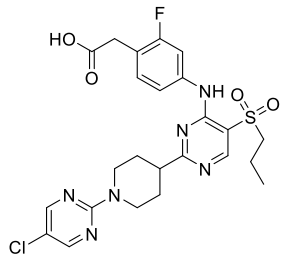
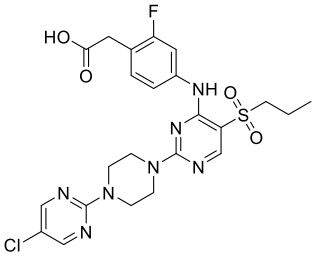
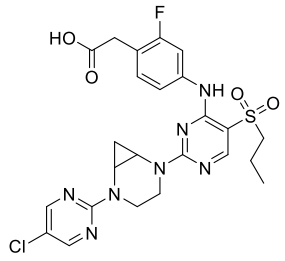
No.	Chemical structure	$[M+H]^+$
219		534.2
220		476.2
221		460.2
222		429.2
223		568.2
224		569.2

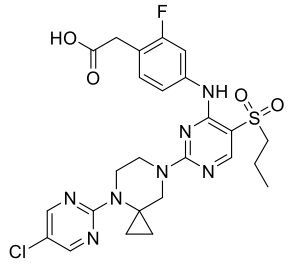
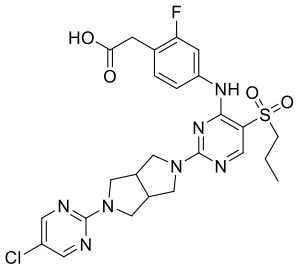
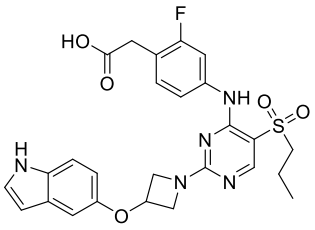
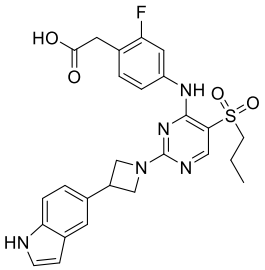
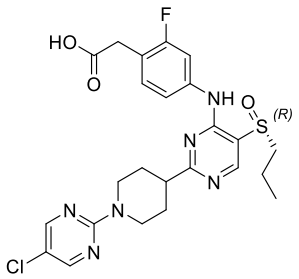
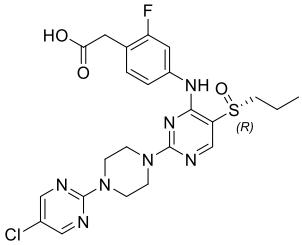
No.	Chemical structure	$[M+H]^+$
225		581.2
226		595.2
227		595.2
228		588.2
229		617.2
230		559.2

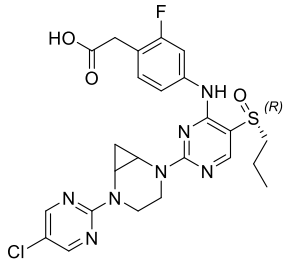
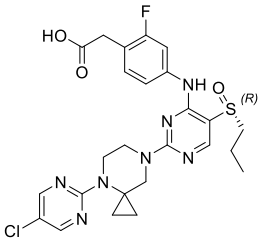
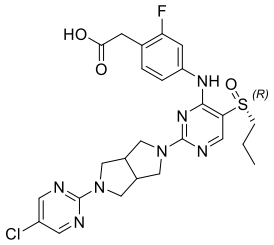
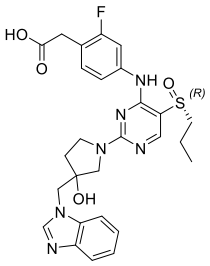
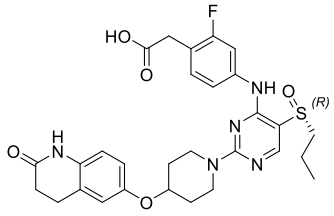
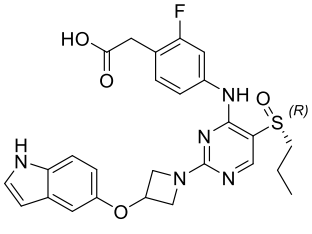
No.	Chemical structure	$[M+H]^+$
231		543.2
232		512.2
233		535.2
234		536.2
235		548.2

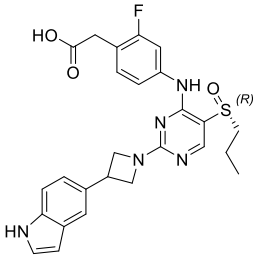
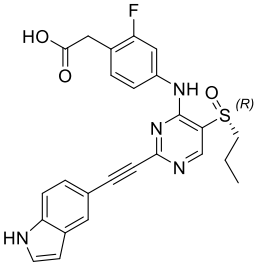
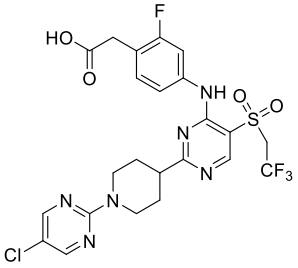
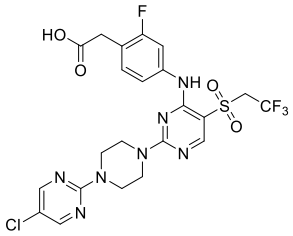
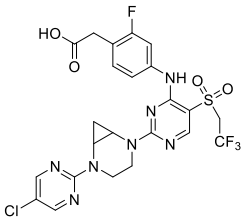
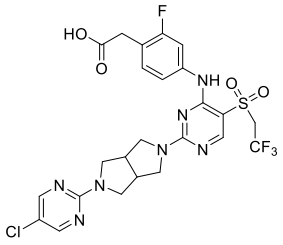
No.	Chemical structure	$[M+H]^+$
236		562.2
237		562.2
238		526.2
239		510.2
240		519.2
241		520.2

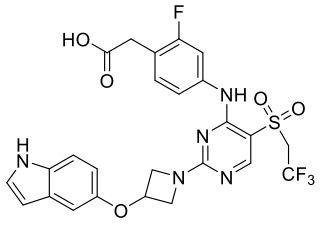
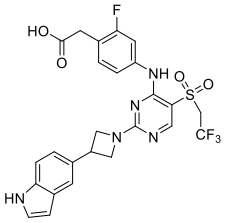
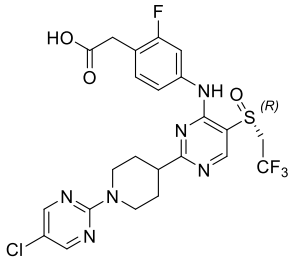
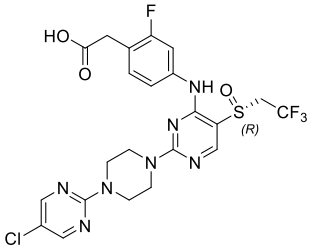
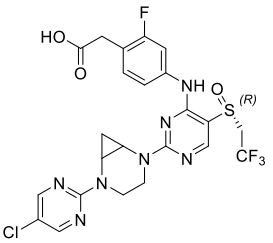
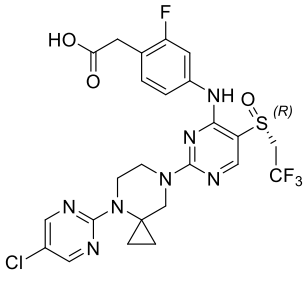
No.	Chemical structure	$[M+H]^+$
242		532.2
243		546.2
244		546.2
245		539.2
246		568.2
247		510.2

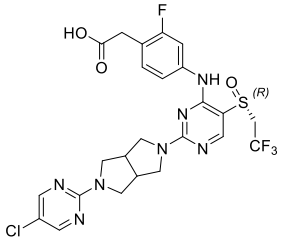
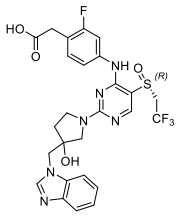
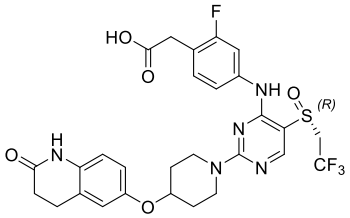
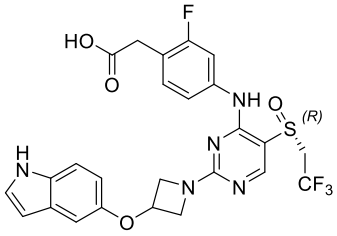
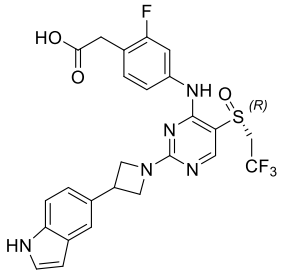
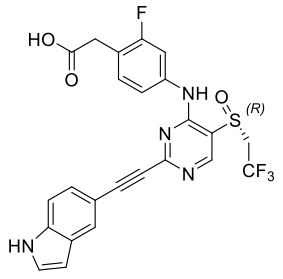
No.	Chemical structure	$[M+H]^+$
248		494.2
249		463.2
250		549.2
251		550.2
252		562.2

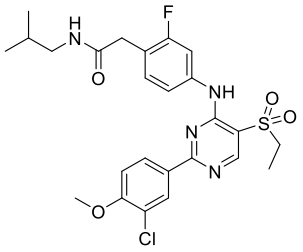
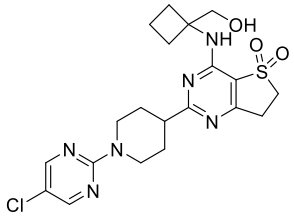
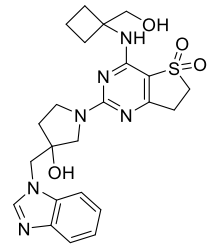
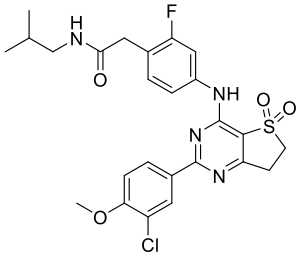
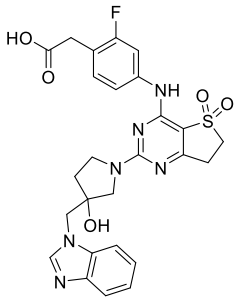
No.	Chemical structure	$[M+H]^+$
253		576.2
254		576.2
255		540.2
256		524.2
257		533.2
258		534.2

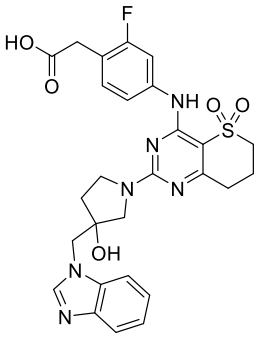
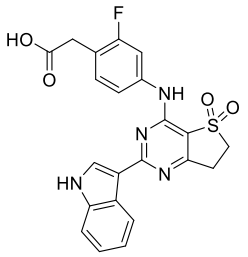
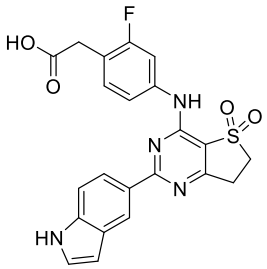
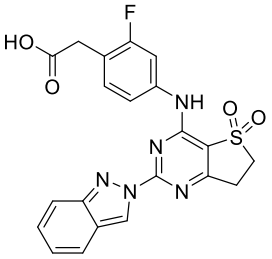
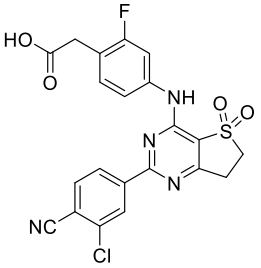
No.	Chemical structure	$[M+H]^+$
259		546.2
260		560.2
261		560.2
262		553.2
263		582.2
264		524.2

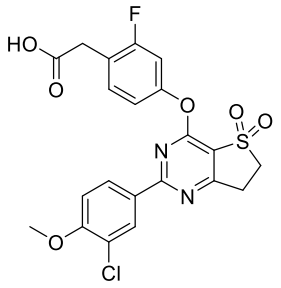
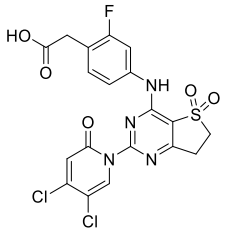
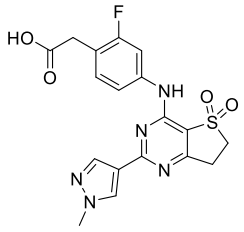
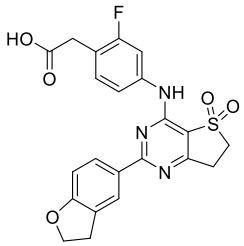
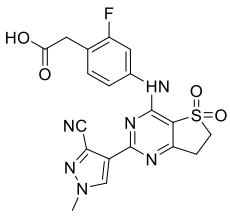
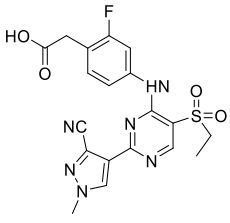
No.	Chemical structure	$[M+H]^+$
265		508.2
266		477.2
267		589.2
268		590.2
269		602.2
270		616.2

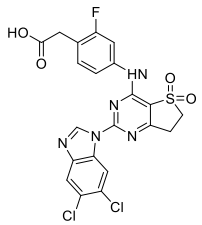
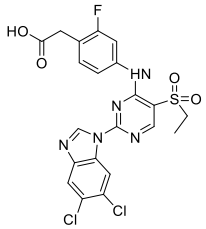
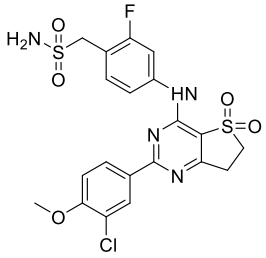
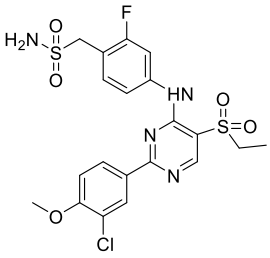
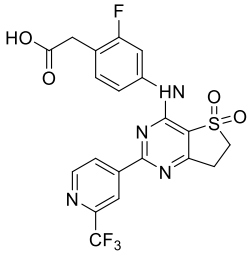
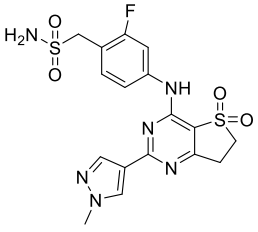
No.	Chemical structure	$[M+H]^+$
271		580.2
272		564.2
273		573.2
274		574.2
275		586.2
276		600.2

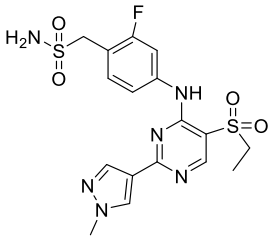
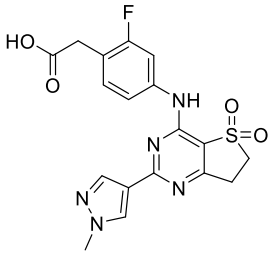
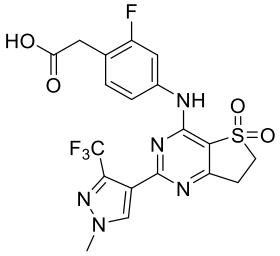
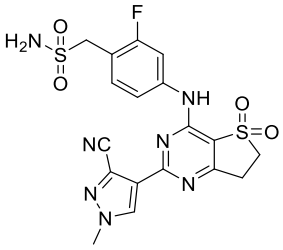
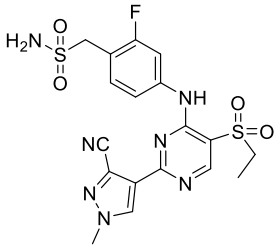
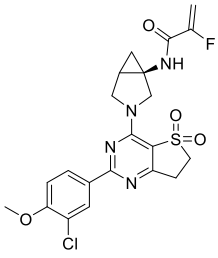
No.	Chemical structure	$[M+H]^+$
277		600.2
278		593.2
279		622.2
280		564.2
281		548.2
282		517.2

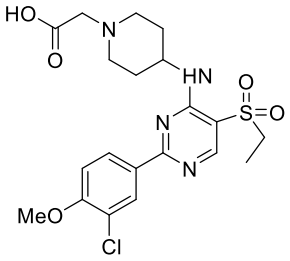
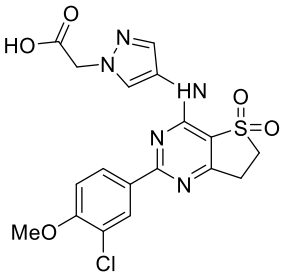
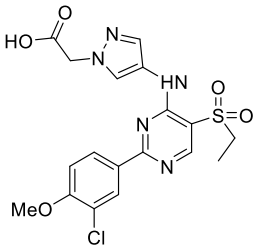
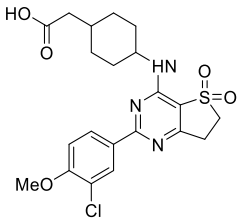
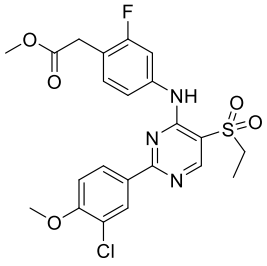
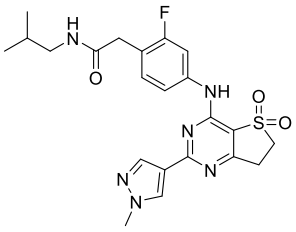
No.	Chemical structure	$[M+H]^+$
283		535.2
284		465.2
285		485.2
286		533.2
287		553.2

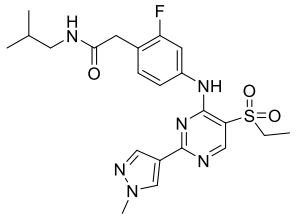
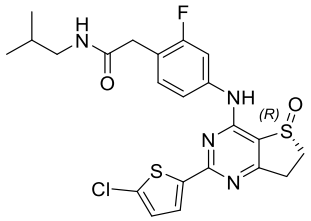
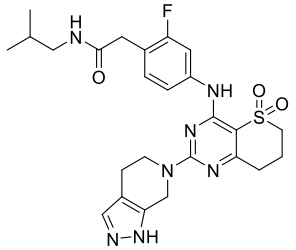
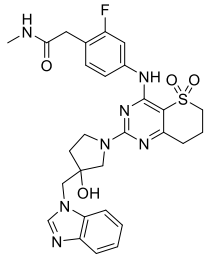
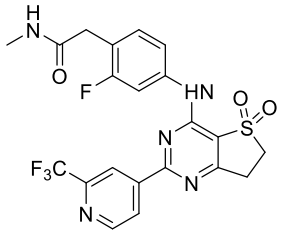
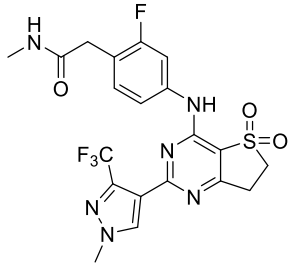
No.	Chemical structure	$[M+H]^+$
288		567.2
289		453.1
290		453.2
291		454.3
292		473.2

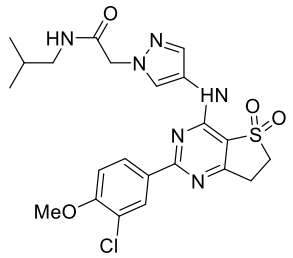
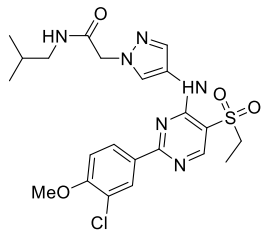
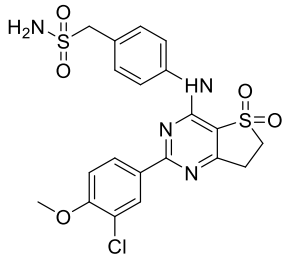
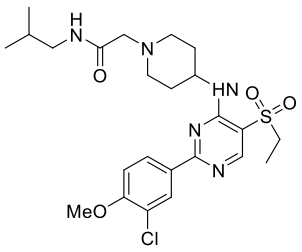
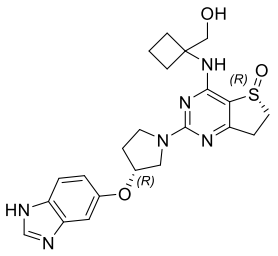
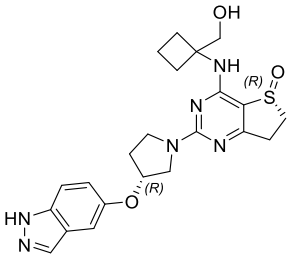
No.	Chemical structure	$[M+H]^+$
293		479.2
294		499.1
295		418.2
296		456.2
297		443.1
298		445.2

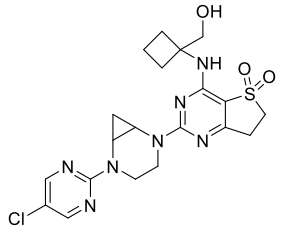
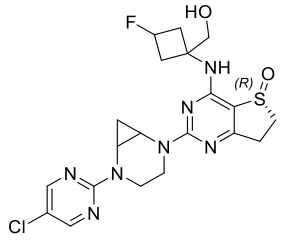
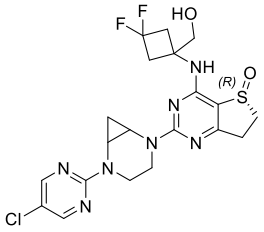
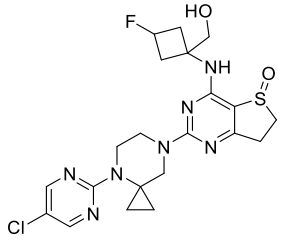
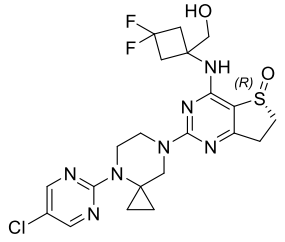
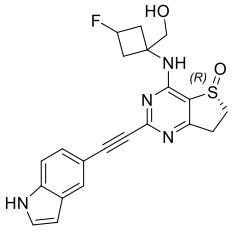
No.	Chemical structure	$[M+H]^+$
299		522.1
300		524.2
307		513.2
308		515.2
311		483.1
313		453.2

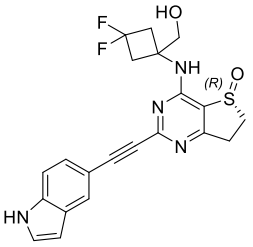
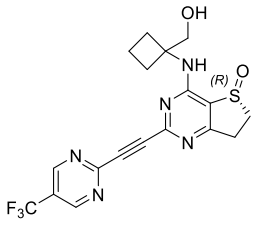
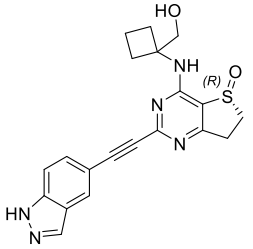
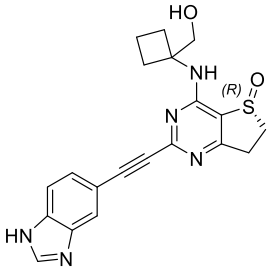
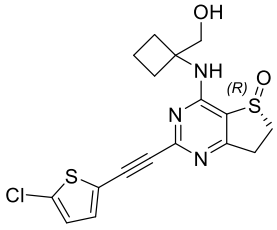
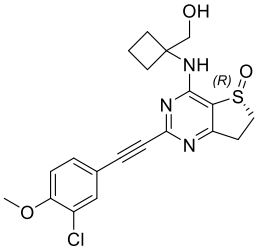
No.	Chemical structure	$[M+H]^+$
314		455.2
315		418.2
317		486.2
319		478.2
320		480.2
346		479.2

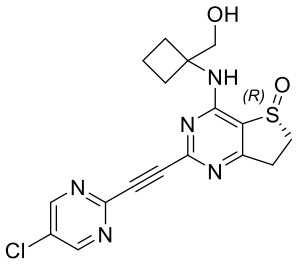
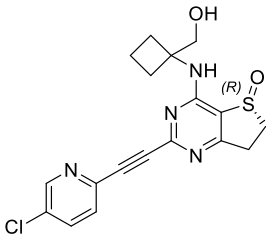
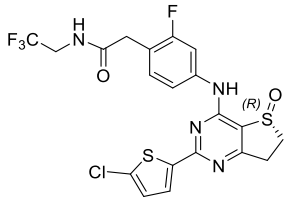
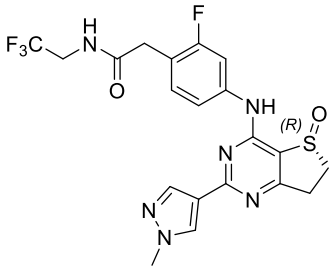
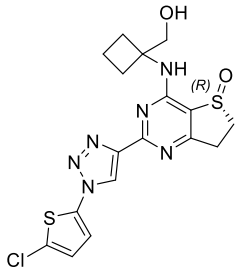
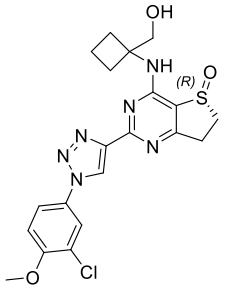
No.	Chemical structure	$[M+H]^+$
347		469.2
349		450.2
350		452.2
351		466.2
352		494.2
353		473.2

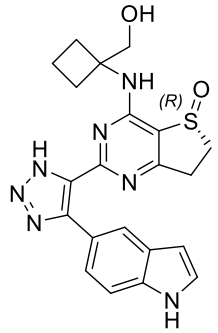
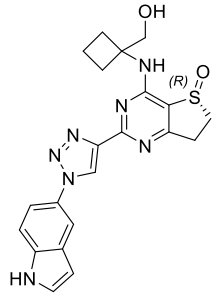
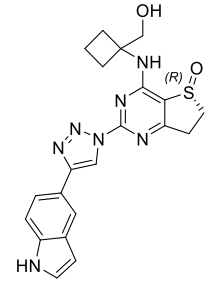
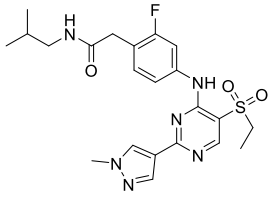
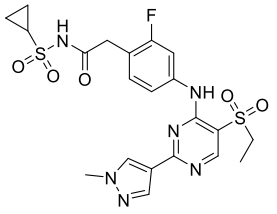
No.	Chemical structure	$[M+H]^+$
354		475.2
355		493.2
356		528.2
357		580.2
358		496.2
359		499.2

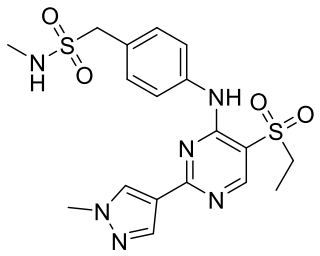
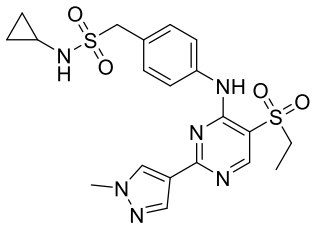
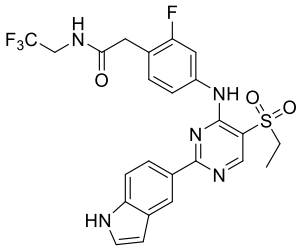
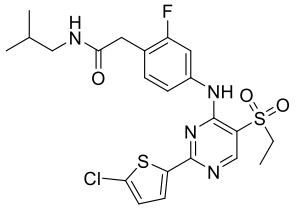
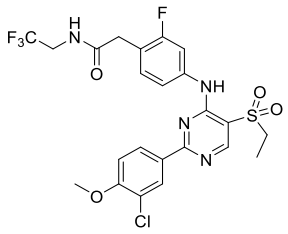
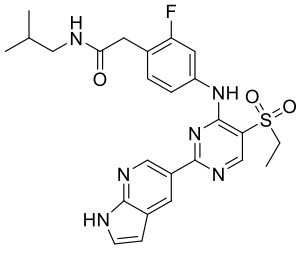
No.	Chemical structure	$[M+H]^+$
360		505.2
361		507.2
362		495.2
363		524.2
365		455.2
366		455.2

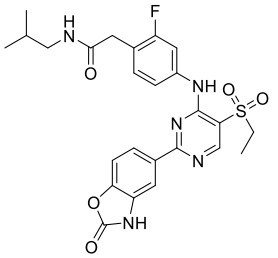
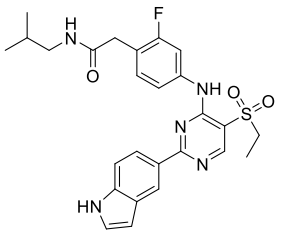
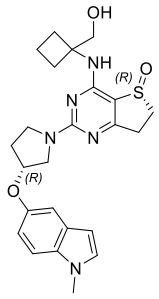
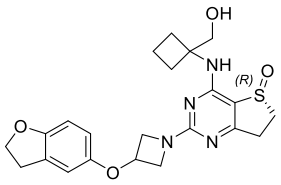
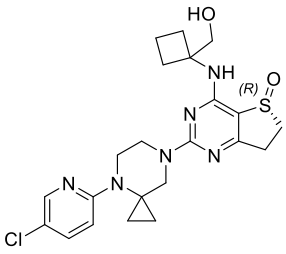
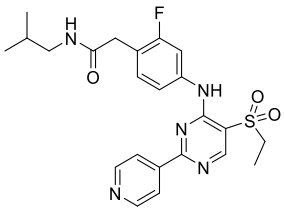
No.	Chemical structure	$[M+H]^+$
367		478.2
368		480.2
369		498.2
370-rac		494.2
371		512.2
372		411.2

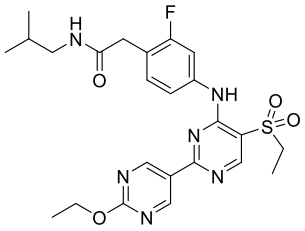
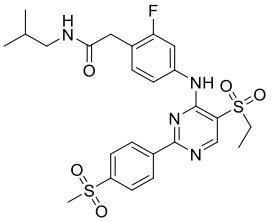
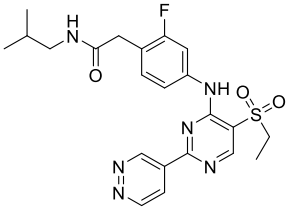
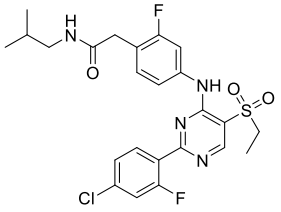
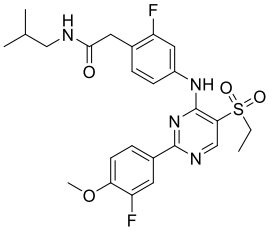
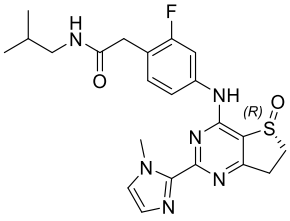
No.	Chemical structure	$[M+H]^+$
373		429.2
374		424.2
375		394.2
376		394.2
377		394.1
378		418.2

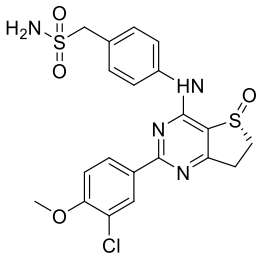
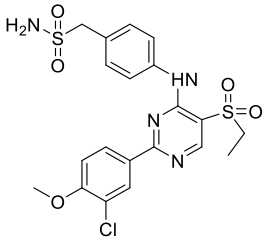
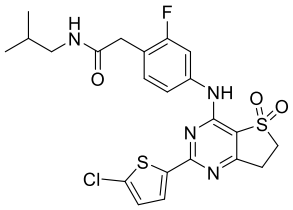
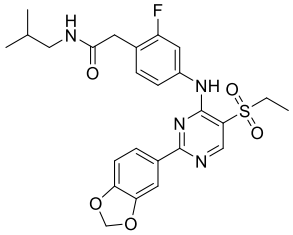
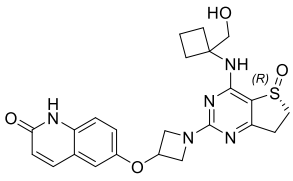
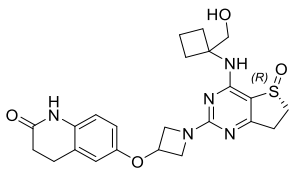
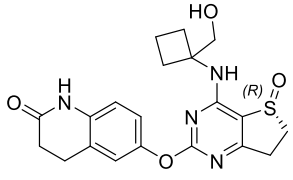
No.	Chemical structure	$[M+H]^+$
379		390.2
380		389.2
387		519.1
398		483.1
404		437.2
405		461.2

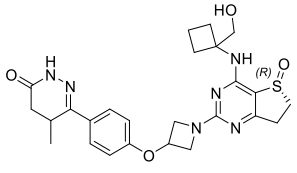
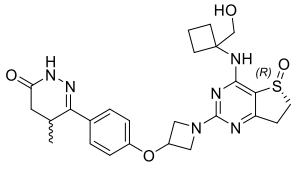
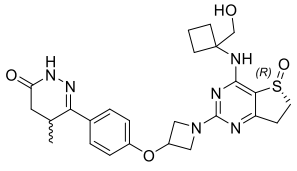
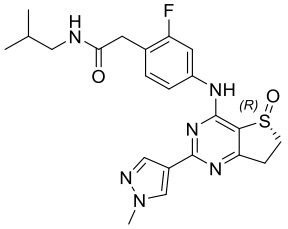
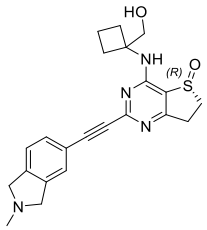
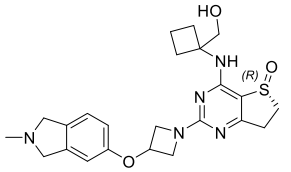
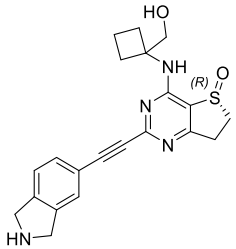
No.	Chemical structure	$[M+H]^+$
406		436.2
407		436.2
408		436.2
409		475.2
410		523.2

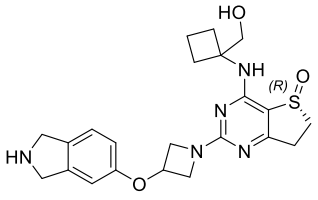
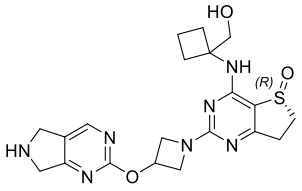
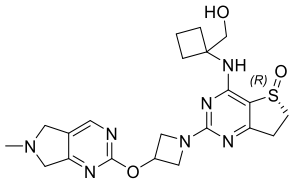
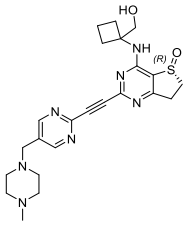
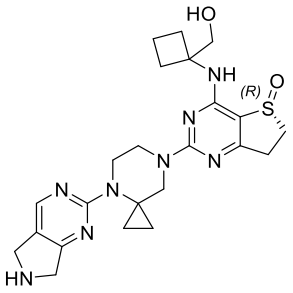
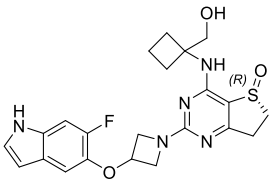
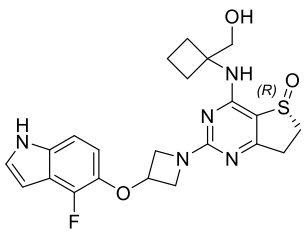
No.	Chemical structure	$[M+H]^+$
411		451.2
412		477.2
413		536.2
415		511.2
416		561.2
417		511.2

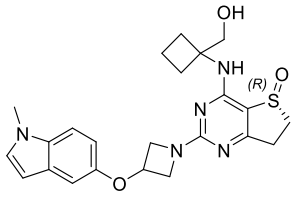
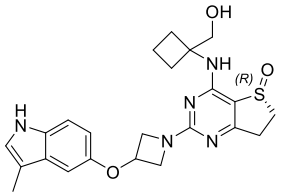
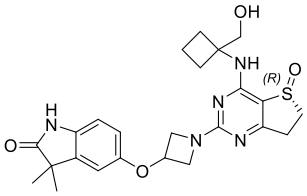
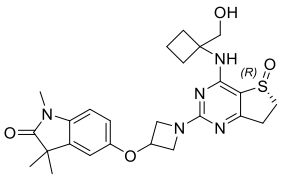
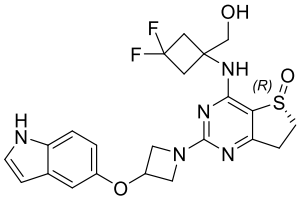
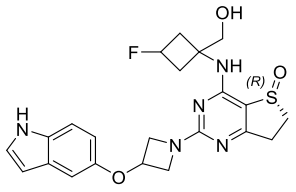
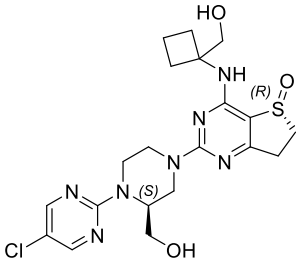
No.	Chemical structure	$[M+H]^+$
418		528.2
419		510.2
420		468.2
421		443.2
422		475.2
423		472.2

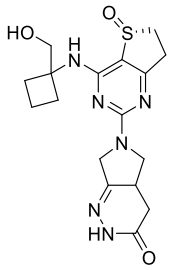
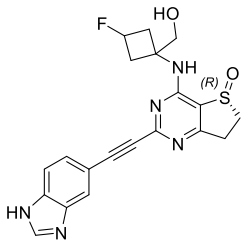
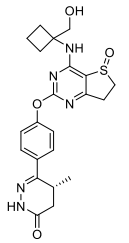
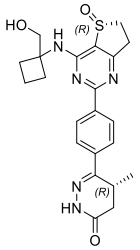
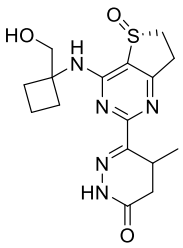
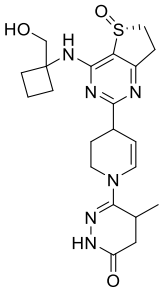
No.	Chemical structure	$[M+H]^+$
424		517.2
425		549.2
426		473.2
427		523.2
428		519.2
429		457.2

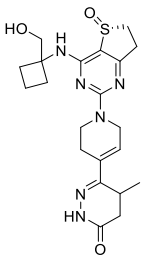
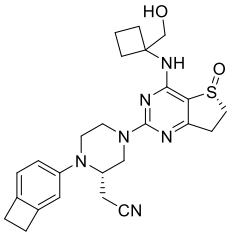
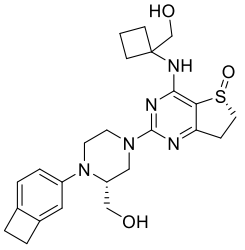
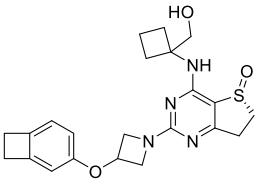
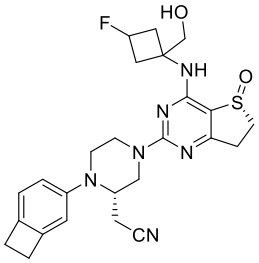
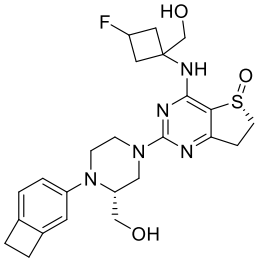
No.	Chemical structure	$[M+H]^+$
430		479.2
431		497.2
432		509.2
433		515.2
434		468.2
435		470.2
436		515.2

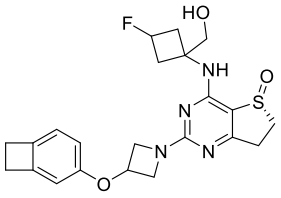
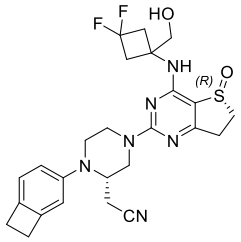
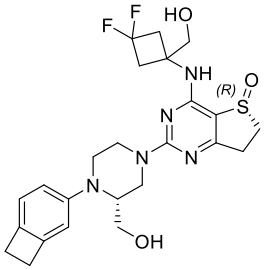
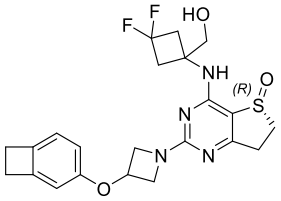
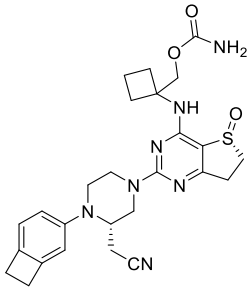
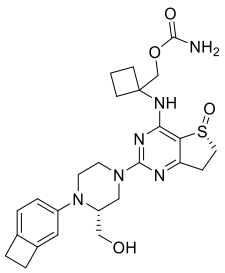
No.	Chemical structure	$[M+H]^+$
437-rac		511.2
437-peak 1		511.2
437-peak 2		511.2
440		467.2
445		409.2
446		456.2
449		395.2

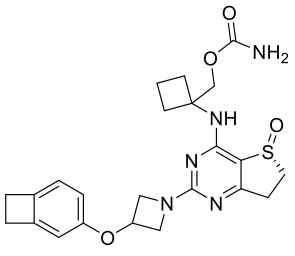
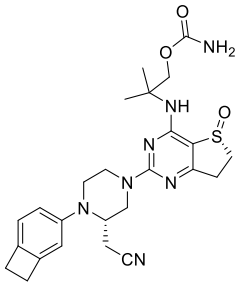
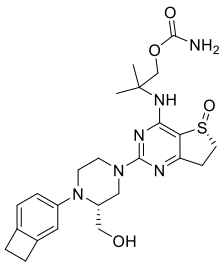
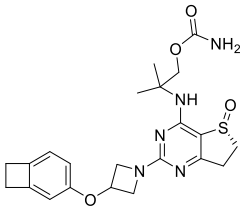
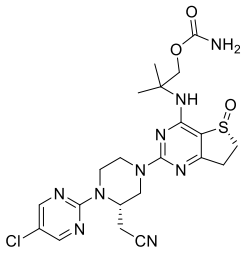
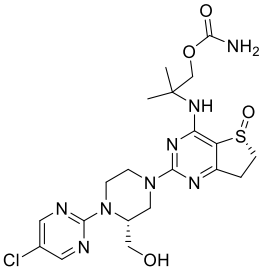
No.	Chemical structure	$[M+H]^+$
450		442.2
453		444.2
454		458.2
455		468.2
456		483.2
458		458.2
459		458.2

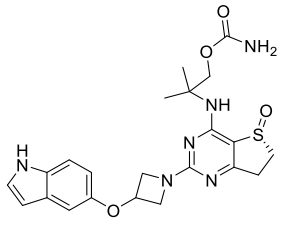
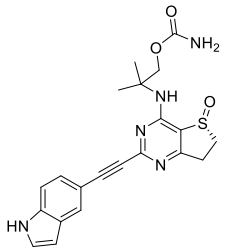
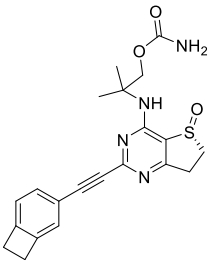
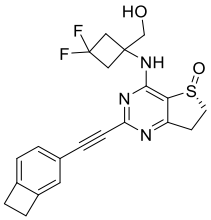
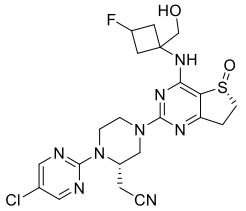
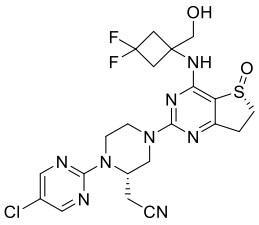
No.	Chemical structure	$[M+H]^+$
460		454.2
461		454.2
462		484.2
463		498.2
464		476.2
465		458.2
466		480.2

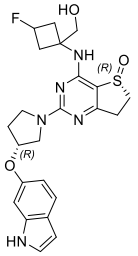
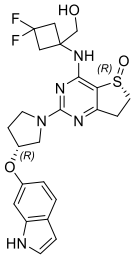
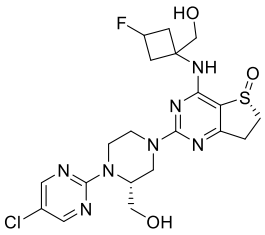
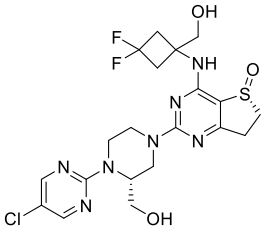
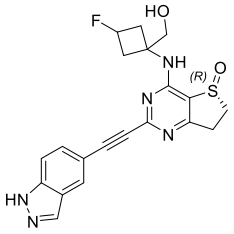
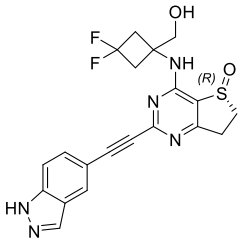
No.	Chemical structure	$[M+H]^+$
467		391.2
470		412.2
472-rac		456.2
473		440.2
476		364.2
477		445.2

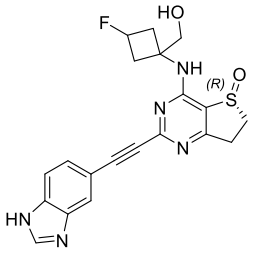
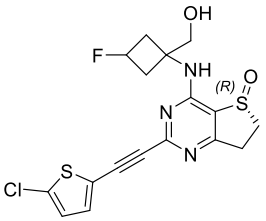
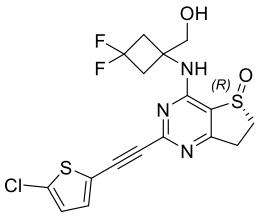
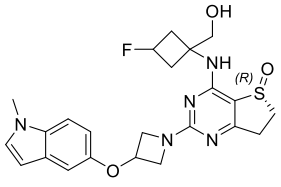
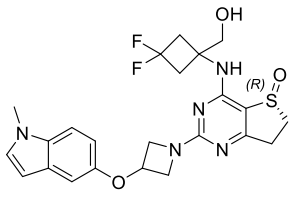
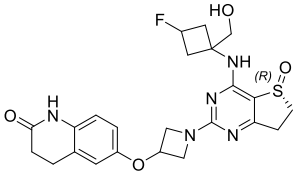
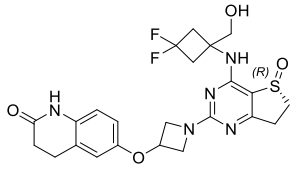
No.	Chemical structure	$[M+H]^+$
478		445.2
479		479.2
480		470.2
481		427.2
482		497.2
483		488.2

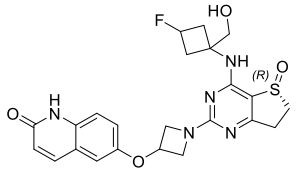
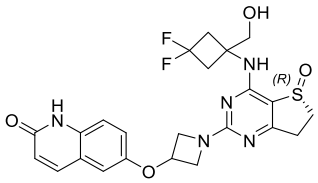
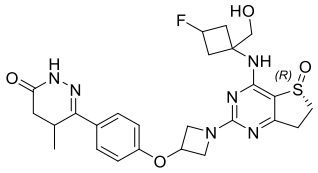
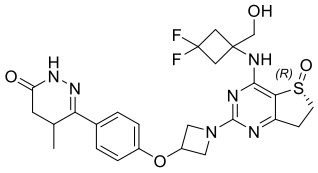
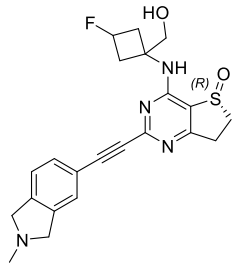
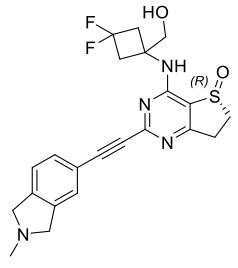
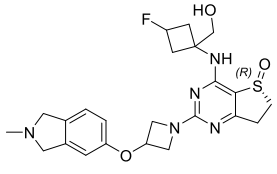
No.	Chemical structure	$[M+H]^+$
484		445.2
485		515.2
486		506.2
487		463.2
488		522.2
489		513.2

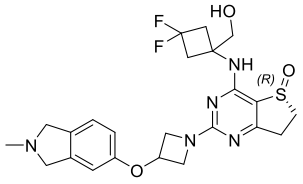
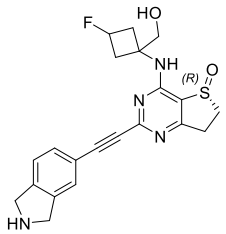
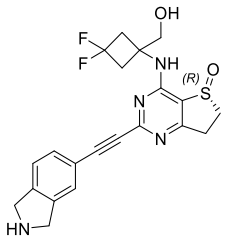
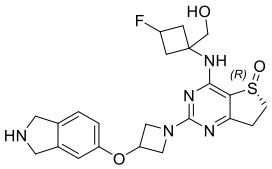
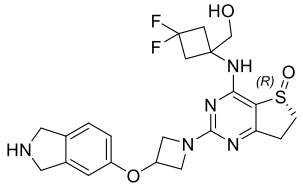
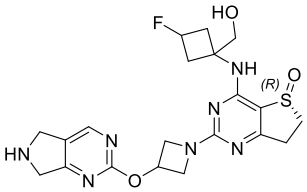
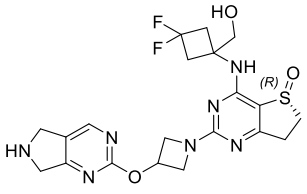
No.	Chemical structure	$[M+H]^+$
490		470.2
491		510.2
492		501.2
493		458.2
494		520.2
495		511.2

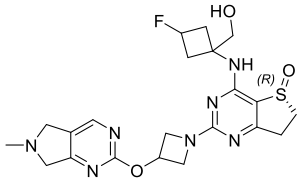
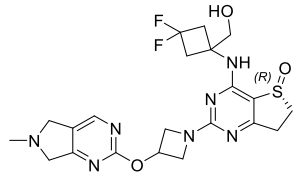
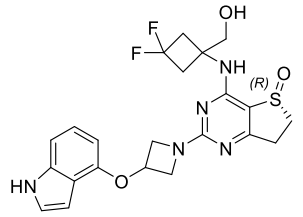
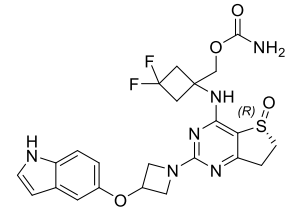
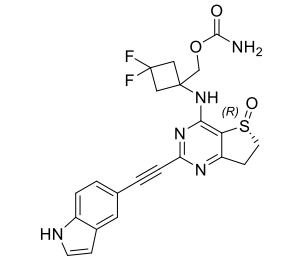
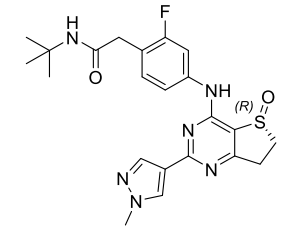
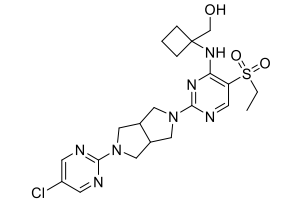
No.	Chemical structure	$[M+H]^+$
496		471.2
497		424.2
498		411.2
499		416.2
520		507.2
521		525.2

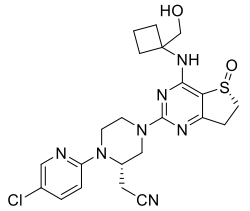
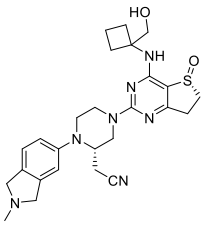
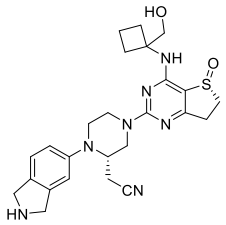
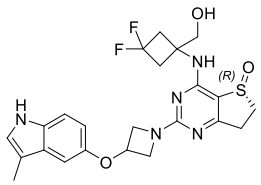
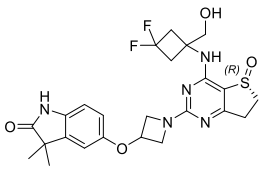
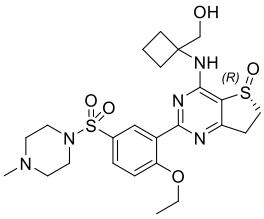
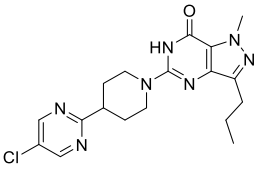
No.	Chemical structure	$[M+H]^+$
522		472.2
523		490.2
524		498.2
525		516.2
526		412.2
527		430.2

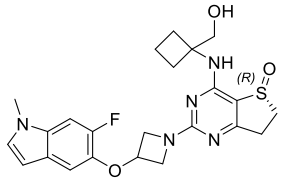
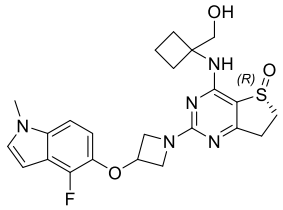
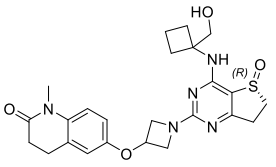
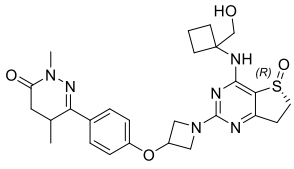
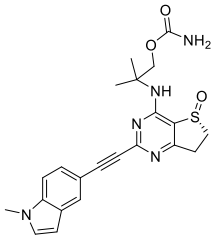
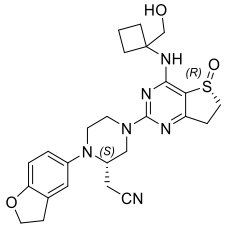
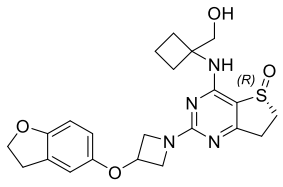
No.	Chemical structure	$[M+H]^+$
528		412.2
529		412.2
530		430.2
531		472.2
532		490.2
533		488.2
534		506.2

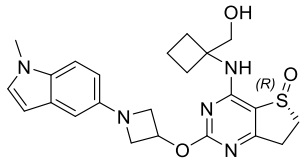
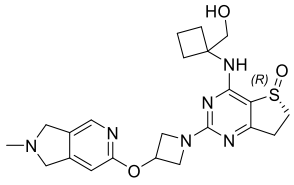
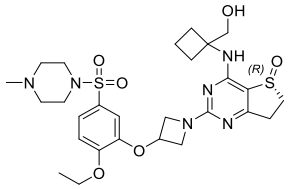
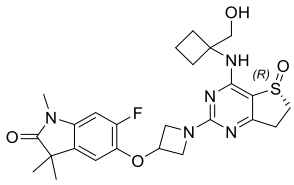
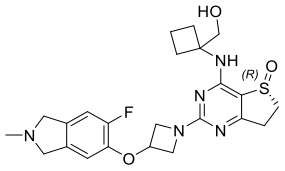
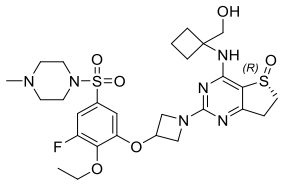
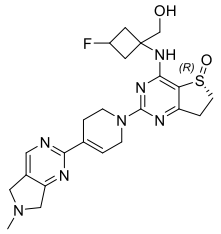
No.	Chemical structure	$[M+H]^+$
535		486.2
536		504.2
537		529.2
538-rac		547.2
539		427.2
540		445.2
541		474.2

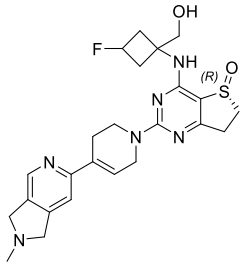
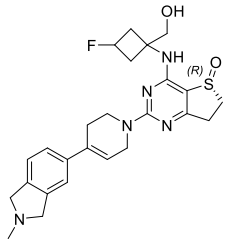
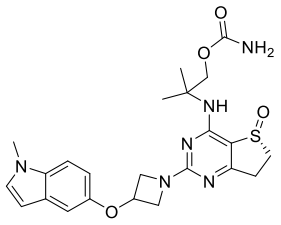
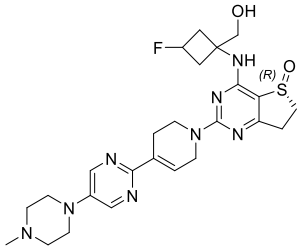
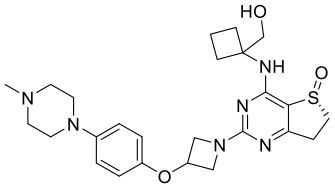
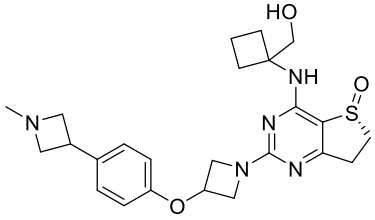
No.	Chemical structure	$[M+H]^+$
542		492.2
543		413.2
544		431.2
545		460.2
546		478.2
547		462.2
548		480.2

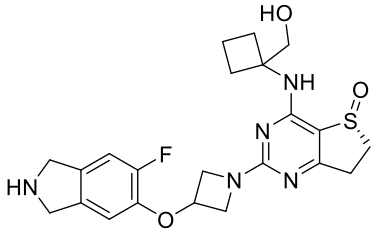
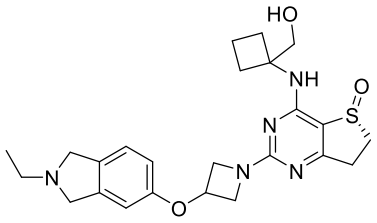
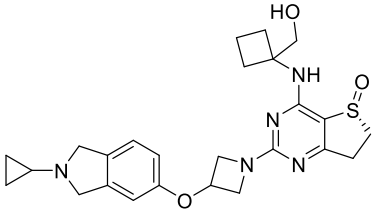
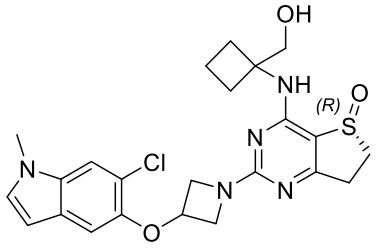
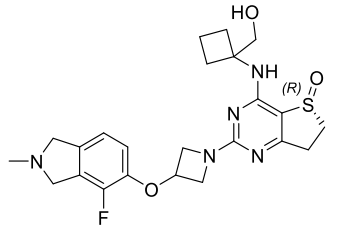
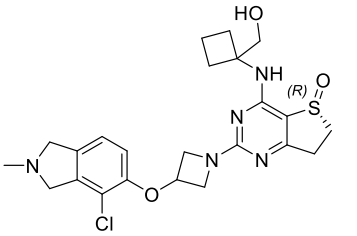
No.	Chemical structure	$[M+H]^+$
549		476.2
550		494.2
578		476.2
579		519.2
584		472.2
590		457.2
596		494.2

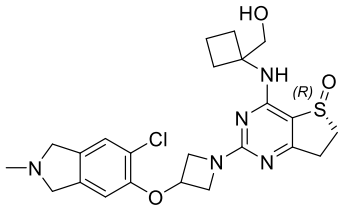
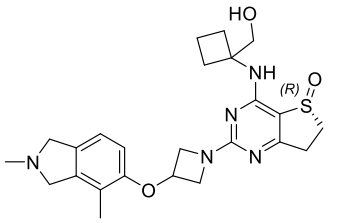
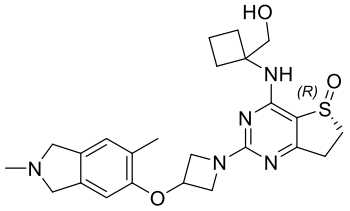
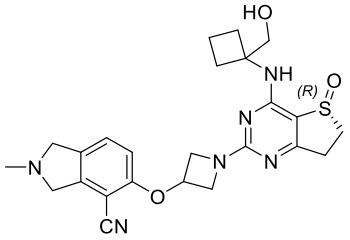
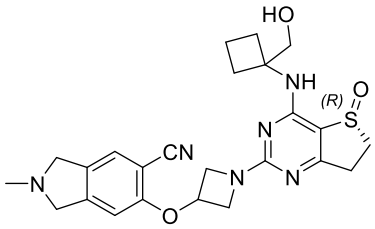
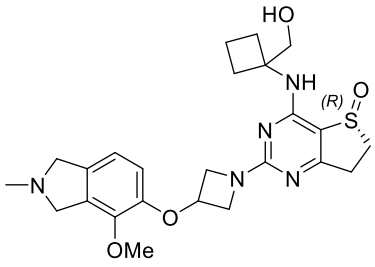
No.	Chemical structure	$[M+H]^+$
597		488.2
598		508.2
599		494.2
605		490.2
606		520.2
607		536.2
608		388.2

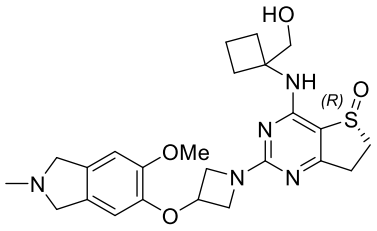
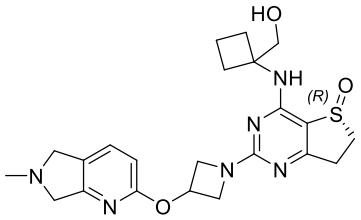
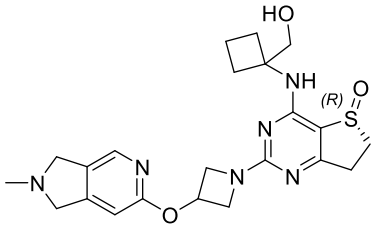
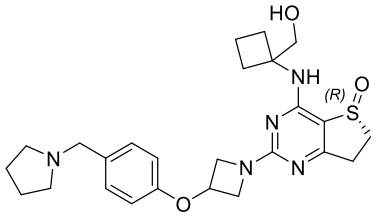
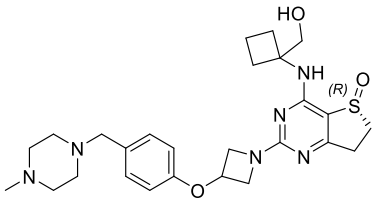
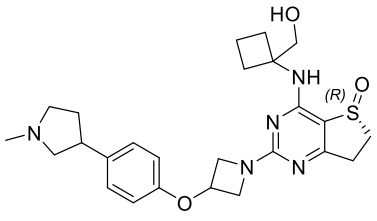
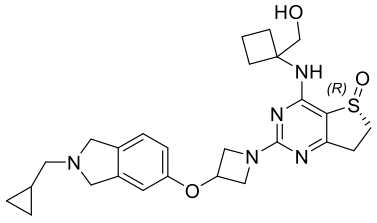
No.	Chemical structure	$[M+H]^+$
609		472.2
610		472.2
611		484.2
612-rac		525.2
613		437.2
614		495.2
615		443.2

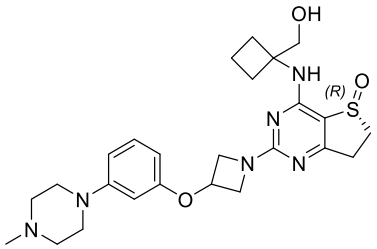
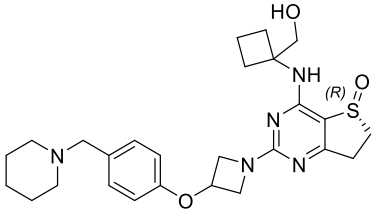
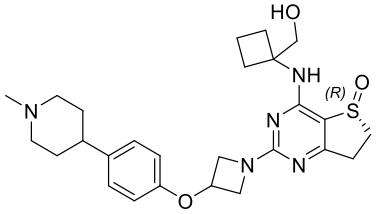
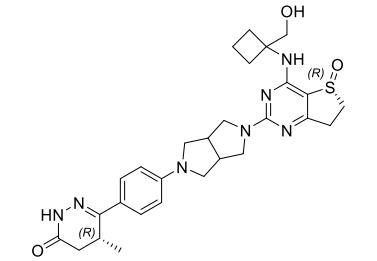
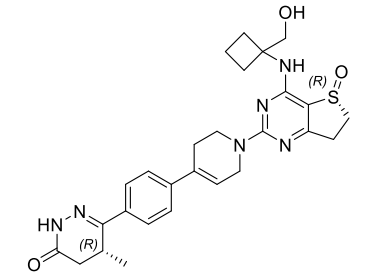
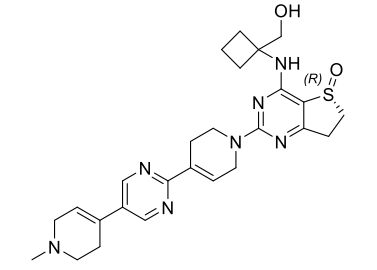
No.	Chemical structure	$[M+H]^+$
616		454.2
617		457.2
618		607.2
619		516.2
620		474.2
621		625.2
622		486.2

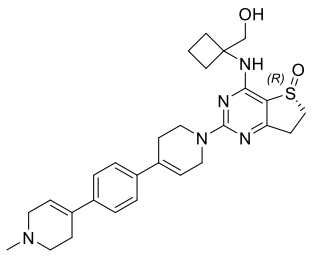
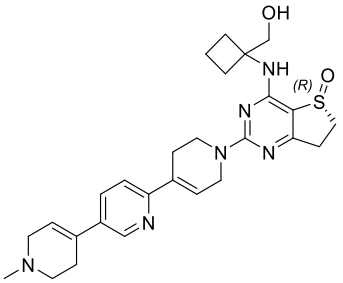
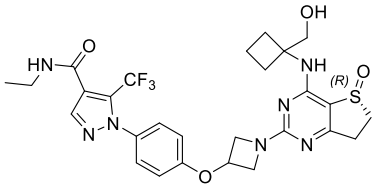
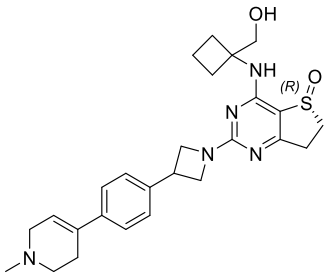
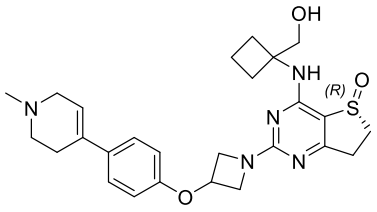
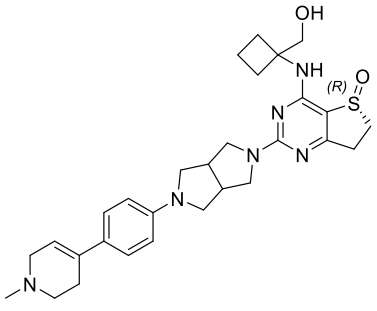
No.	Chemical structure	$[M+H]^+$
623		485.2
624		484.2
625		485.2
626		529.2
627		499.2
628		470.2

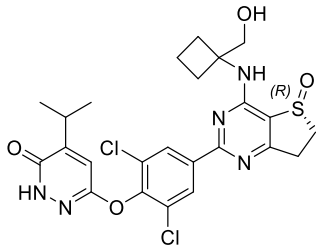
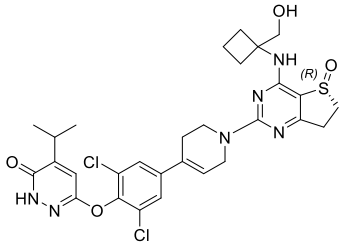
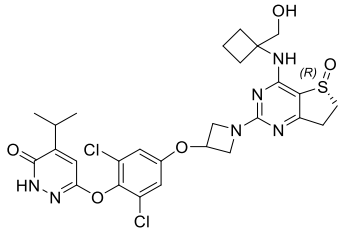
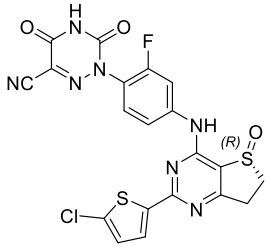
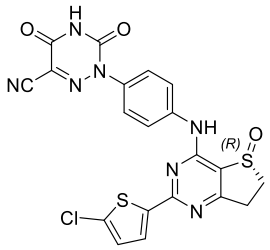
No.	Chemical structure	$[M+H]^+$
629		460.2
630		470.2
631		482.2
632		488.2
633		474.2
634		490.2

No.	Chemical structure	$[M+H]^+$
635		490.2
636		470.2
637		470.2
638		481.2
639		481.2
640		485.2

No.	Chemical structure	$[M+H]^+$
641		486.2
642		457.2
643		457.2
644		484.2
645		513.2
646		484.2
647		496.2

No.	Chemical structure	$[M+H]^+$
648		499.2
649		498.2
650		498.2
651		550.2
652		521.2
653		508.2

No.	Chemical structure	$[M+H]^+$
654		506.2
655		507.2
656		606.2
657		480.2
658		496.2
659		535.2

No.	Chemical structure	$[M+H]^+$
660		550.2
661		631.2
662		621.2
663		516.2
664		498.2

Example 2: Inhibition Assay for Enzymatic Activity of PDE4B2/PDE4D2

The inhibition of PDE4B2/4D2 enzymatic activity by the compounds was assayed by the FP method. PDE4B2/PDE4D2 (BPS, Cat: 60042/60040) enzyme and substrate (FAM-cyclic adenosine monophosphate) (BPS, Cat: 60200) solutions were prepared in a reaction buffer (1× IMAP reaction buffer containing 0.1% BSA with 1 mM DTT). The final working concentrations of PDE4B2, PDE4D2, and FAM-cyclic adenosine monophosphate were 0.0075

nM, 0.1 nM, and 100 nM, respectively. The positive control, MX02018 (BI1015550), was initially tested at a concentration of 3 μM against PDE4B2/PDE4D2, and the 3-fold dilution was performed to obtain 10 concentration doses. The test compounds were initially prepared at a concentration of 3 μM against PDE4B2/PDE4D2, and the 3-fold dilution was performed to obtain 10 concentration doses.

The stock solution of each test compound was heated and vortexed and shaken to be mixed well to prepare a working solution with an initial concentration of 300 μM, and the 3-fold serial dilution was performed to obtain working solutions with 10 different final concentrations. This part of the reaction was performed in the source plate. 0.05 μL of the compound diluted in 100% DMSO in the source plate was transferred to a 384-well plate (Corning4514) by using acoustic liquid-transfer technology (Echo 655) and centrifuged at 1000 rpm for 1 min, with the final concentration of DMSO being 1%; 2.5 μL of PDE4B2/PDE4D2 enzyme solution was transferred to the 384-well reaction plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 10 min; 2.5 μL of substrate (FAM-cyclic adenosine monophosphate) solution was transferred to the 384-well reaction plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 60 min; 15 μL of the binder mixture was transferred to the 384-well plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 60 min; FP signals were read using BMG (PHERAstar FSX), and IC_{50} values were obtained and non-linear regression curve fitting was performed using GraphPad Prism software.

The activity test results of some of the example compounds are summarized in Table 2 below:

Table 2: Activity test results of some example compounds

Example compound	**IC_{50} (nM) / PDE4B2**	**IC_{50} (nM) / PDE4D2**
MX02010	12.03	30.37
MX02128	1.57	13.27
MX02024	0.75	1.47
MX02129	1.73	1.95
MX02016	4.34	10.11
MX02122	2.56	48.99
MX02029	6.34	9.00
MX02043	10.19	21.03

Example compound	IC_{50} (nM) / PDE4B2	IC_{50} (nM) / PDE4D2
MX02026	8.94	19.82
MX02021	2.88	34.50
MX02089	5.29	8.95
MX02053	13.95	27.08
MX02058	1.21	12.53
MX02090	9.62	18.79
MX02020	2.11	24.90
MX02025	6.16	68.30
MX02126	4.41	36.51
MX02075	2.83	21.45
MX02044	64.89	729.60
MX02164	21.79	342.50
MX02165	4.02	310.10
MX02166	0.77	1391.00
MX02115	16.22	135.80
MX02156	0.53	13.72
MX02096	76.30	1805.00
MX02078	223.60	1797.00
MX02161	6.76	912.40
MX02147	194.30	>3000
MX02159	0.084	17.88
MX02180	28.58	2392.00
MX02206	22.80	802.80
MX02285	7.70	1523.00

Example compound	IC_{50} (nM) / PDE4B2	IC_{50} (nM) / PDE4D2
MX02287	26.11	2708.00
MX02170	13.33	405.30
MX02283	27.69	267.00
MX02355	0.39	1.58
MX02356	1.42	13.00
MX02357	35.46	219.10
MX02365	3.06	21.19
MX02366	2.44	19.36
MX02375	4.85	56.92
MX02377	11.19	146.00
MX02381-rac	30.05	285.60
MX02380	62.34	653.90
MX02387	9.75	44.60
MX02419	13.85	237.00
MX02422	1.31	16.13
MX02418	9.61	133.90
MX02376	7.79	80.66
MX02423	33.45	283.10
MX02435	1.95	16.70
MX02434	2.11	20.28
MX02440	9.99	64.89
MX02437-rac	2.60	18.10
MX02460	1.24	11.33
MX02370-rac	4.85	50.61

Example compound	IC_{50} (nM) / PDE4B2	IC_{50} (nM) / PDE4D2
MX02371	7.83	118.30
MX02464	3.02	58.52
MX02461	2.20	17.33
MX02462	2.55	18.40
MX02373	13.99	131.70
MX02465	2.45	23.10
MX02012	17.79	163.60
MX02446	17.60	201.50
MX02466	72.82	902.70
MX02458	0.52	12.64
MX02463	2.38	30.55
MX02437-peak1	2.09	20.45
MX02437-peak2	2.42	16.80
MX02532	3.84	38.16
MX02459	1.35	9.43
MX02473	3.17	20.88
MX02578	4.39	39.48
MX02605	11.50	81.58
MX02606	11.43	70.89
MX02521	28.84	293.00
MX02538-rac	9.74	56.03
BI1015550	14.67	76.99

The above experimental results show that the compounds of the present disclosure have excellent inhibitory activity against PDE4B, and even the IC_{50} values of compounds such as MX02024, MX02156, MX02159, MX02166, MX02355, MX02609, MX02651, MX02652,

and MX02655 can reach the pmol level. Further, it can be seen from the above experimental results that the compounds with the novel structures disclosed herein have excellent PDE 4B/PDE 4D selectivity. By calculating the IC_{50} ratio of PDED2 to PDEB2, the results are as follows:

5

Example compound	Selective PDE4D2/PDE4B2
MX02096	23.66
MX02122	19.14
MX02156	25.86
MX02159	212.6
MX02161	134.89
MX02165	77.14
MX02166	1806.50
MX02170	30.41
MX02180	83.69
MX02188	119.82
MX02206	35.21
MX02285	197.87
MX02287	103.72
MX02442	37.46
MX02450	23.54
MX02458	24.31
MX02464	19.38
MX02596	18.60

Example 3: Inhibition Assay for Enzymatic Activity of Other Targets

3.1. Inhibition assay for enzymatic activity of PDE3A/3B

The inhibition of PDE3A/3B enzymatic activity by the compounds was assayed by the FP

method. PDE3A (Sino Biological, Cat: 11908-H20B1), PDE3B (BPS, Cat: 60031) enzyme, and substrate (FAM-cyclic adenosine monophosphate) (BPS, Cat: 60200) solutions were prepared in a reaction buffer (1× IMAP reaction buffer containing 0.1% BSA with 1 mM DTT). The final concentrations of PDE3A, PDE3B, and FAM-cyclic adenosine monophosphate were 1 nM, 0.3 nM, and 100 nM, respectively. The positive control, Cilostamide, was initially tested at a concentration of 10 μM against PDE3A/3B, and the 3-fold dilution was performed to obtain 10 doses. The test compounds were initially prepared at a concentration of 10 μM against PDE3A/3B, and the 3-fold dilution was performed to obtain 10 doses. The stock solution of each test compound was heated and vortexed and shaken to be mixed well, 6 μL of the compound was added to 54 μL of DMSO, and the mixture was mixed well to prepare a working solution with an initial concentration of 1 mM. The 3-fold serial dilution was performed to obtain working solutions with 10 different final concentrations. This part of the reaction was performed in the source plate. 0.05 μL of the compound diluted in 100% DMSO in the source plate was transferred to a 384-well plate (Corning4514) by using acoustic liquid-transfer technology (Echo 655) and centrifuged at 1000 rpm for 1 min, with the final concentration of DMSO being 1%; 2.5 μL of PDE3A/3B enzyme solution was transferred to the 384-well reaction plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 10 min; 2.5 μL of substrate (FAM-cyclic adenosine monophosphate) solution was transferred to the 384-well reaction plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 60 min; 15 μL of the binder mixture was transferred to the 384-well plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 60 min; finally, FP signals were read using BMG (PHERAstar FSX). IC_{50} values were obtained and non-linear regression curve fitting was performed using GraphPad Prism software.

3.2. Inhibition assay for enzymatic activity of PDE5A1

The inhibition of PDE5A1 enzymatic activity by the compounds was assayed by the FP method. PDE5A1 (BPS, Cat: 60050) enzyme and substrate (FAM-cyclic guanosine monophosphate) (BPS, Cat: 60201) solutions were prepared in a reaction buffer (1× IMAP reaction buffer containing 0.1% BSA with 1 mM DTT). Final concentrations of PDE5A1 and FAM-cyclic guanosine monophosphate were 1 nM and 100 nM, respectively. The positive control, Sildenafil citrate, was initially tested at a concentration of 1 μM against PDE5A1, and the 3-fold dilution was performed to obtain 10 doses. The test compounds were initially prepared at a concentration of 10 μM against PDE5A1, and the 3-fold dilution was performed to obtain 10 doses. The stock solution of each test compound was heated and vortexed and shaken to be mixed well, 6 μL of the compound was added to 54 μL of DMSO, and the mixture was mixed

well to prepare a working solution with an initial concentration of 1 mM. The 3-fold serial dilution was performed to obtain working solutions with 10 different final concentrations. This part of the reaction was performed in the source plate. 0.05 μL of the compound diluted in 100% DMSO in the source plate was transferred to a 384-well plate (Corning4514) by using acoustic liquid-transfer technology (Echo 655) and centrifuged at 1000 rpm for 1 min, with the final concentration of DMSO being 1%; 2.5 μL of PDE5A1 enzyme solution was transferred to the 384-well reaction plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 10 min; 2.5 μL of substrate (FAM-cyclic guanosine monophosphate) solution was transferred to the 384-well reaction plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 60 min; 15 μL of the binder mixture was transferred to the 384-well plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 60 min; finally, FP signals were read using BMG (PHERAstar FSX). IC_{50} values were obtained and non-linear regression curve fitting was performed using GraphPad Prism software.

3.3. Inhibition assay for enzymatic activity of PDE1A/2A

The inhibition of PDE1A/2A enzymatic activity by the compounds was assayed by the FP method. PDE1A (BPS, Cat: 60010), PDE2A (BPS, Cat: 60020) enzyme and substrate (FAM-cyclic adenosine monophosphate) (BPS, Cat: 60201) solutions were prepared in a reaction buffer (1× IMAP reaction buffer containing 0.1% BSA with 1 mM DTT). The final concentrations of PDE1A, PDE2A, and FAM-cyclic guanosine monophosphate were 2 nM, 0.5 nM, and 100 nM, respectively. The positive control, Bay 60-7550, was initially tested at a concentration of 100 μM against PDE1A, and the 3-fold dilution was performed to obtain 10 doses. The positive control, Bay 60-7550, was initially tested at a concentration of 100 μM against PDE2A, and the 3-fold dilution was performed to obtain 10 doses. The test compounds were initially prepared at a concentration of 10 μM against PDE1A/2A, and the 3-fold dilution was performed to obtain 10 doses. The stock solution of each test compound was heated and vortexed and shaken to be mixed well, 6 μL of the compound was added to 54 μL of DMSO, and the mixture was mixed well to prepare a working solution with an initial concentration of 1 mM. The 3-fold serial dilution was performed to obtain working solutions with 10 different final concentrations. This part of the reaction was performed in the source plate. 0.05 μL of the compound diluted in 100% DMSO in the source plate was transferred to a 384-well plate (Corning4514) by using acoustic liquid-transfer technology (Echo 655) and centrifuged at 1000 rpm for 1 min, with the final concentration of DMSO being 1%; 2.5 μL of PDE1A/2A enzyme solution was transferred to the 384-well reaction plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 10 min; 2.5 μL of substrate (FAM-cyclic adenosine monophosphate)

solution was transferred to the 384-well reaction plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 60 min; 15 μL of the binder mixture was transferred to the 384-well plate, centrifuged at 1000 rpm for 1 min, and incubated at 25 °C for 60 min; finally, FP signals were read using BMG (PHERAstar FSX). IC_{50} values were obtained and non-linear regression curve fitting was performed using GraphPad Prism software.

The activity test results of the example compounds of the present disclosure are as follows:

Example compound	IC_{50} (nM) / PDE3B	IC_{50} (nM) / PDE5A
MX02437	285	
MX02473	5.4	
MX02538	436	
MX02652	47	
MX02618		55.2

Example 4: Tissue Distribution Assay

4.1. Animals

Animal strain	CD1
Sex	♂
Week age	6-8 weeks
Body weight	20-30 g
Environment	Animals were housed in a controlled environment (with the temperature set at 20-25 °C and relative humidity at 40-70%). A 12-hour light/12-hour dark cycle was maintained, except for interruptions due to study-related procedures.

4.2. Experimental design

Mice in the fasting group were fasted for 12 h before administration,
and allowed free access to food 4 h after administration.

Compound	Administration Regimen	Administration dose (mg/kg)	Administration concentration (mg/mL)	Administration volume (mL/kg)	Number of animals (mice)	Drug vehicle	Fasting status
MX02058	PO	10	1	10	N=3	10% DMSO + 20% Solutol HS-15 + 70% H_2O	Fasting
MX02473	PO	10	1	10	N=3		Fasting
MX02159	PO	10	1	10	N=3		Fasting

4.3. Sample collection and analysis

(1) Plasma

Blood collection volume: 0.1 mL

Blood collection mode: orbital venous plexus

Anticoagulant: EDTA-K_2

Blood collection time: 30 min after administration of MX02058; 30 min after administration of MX02473; 1 h after administration of MX02159

The collected blood samples were transferred to microcentrifuge tubes containing EDTA-K_2 anticoagulant and centrifuged at 4000 g for 5 min at 4 °C. The supernatants were then collected and stored in a refrigerator at -75±15 °C.

(2) Tissue

Collected tissues: brain, heart, liver, lung, kidney, and prostate

Tissue collection time points: 30 min after administration of MX02058, 30 min after administration of MX02473, and 1 h after administration of MX02159. The tissues were taken out, washed with normal saline, weighed, homogenized with 1:4 PBS, and stored in a refrigerator at -75±15 °C.

LC-MS/MS analysis was performed after pretreatment.

4.4. Animal treatment

After the end of the experiment, all the animals were euthanized using a CO_2 euthanasia device and placed in a refrigerator at -20 °C for unified treatment by the relevant institutions.

4.5. Experimental results

The above experimental results are detailed in Table A, which indicates that the compounds of the present disclosure have specific tissue distribution. For example, compound MX02159 exhibited specific distribution to liver tissues, with the liver tissue exposure of PO (10 mg/kg, mice) being 3710 ng/g, which was 10 times the plasma concentration and 300 times the brain tissue concentration, and thus has potential application value for the development of liver-targeted oral drugs for hepatic fibrosis and NASH. Compound MX02473 exhibited significantly higher distribution in kidney tissues and prostate tissues compared to other tissues, while showing minimal distribution in the brain, and thus has potential application value for the development of kidney and prostate-related diseases.

Table A: Results of tissue distribution assay in Example 4

Tissue distribution study (mice, N = 3, PO, 10 mg/kg)													
Compound	Plasma (ng/mL)	Brain (ng/g)	Brain/plasma concentration ratio	Lung (ng/g)	Lung/plasma concentration ratio	Liver (ng/g)	Liver/plasma concentration ratio	Kidney (ng/g)	Kidney/plasma concentration ratio	Heart (ng/g)	Heart/plasma concentration ratio	Prostate (ng/g)	Prostate/plasma concentration ratio
MX02058	1410±101	24±3.1	0.0173	769±112	0.546	3150±469	2.23	2030±359	1.44	934±189	0.662	457±20	0.324
MX02473	442±119	15.3±8.68	0.0346	455±121	1.03	416±184	0.942	2177±866	4.92	775±281	1.75	1231	2.79
MX02159	352±77.5	12.5±1.87	0.0355	189±56.3	0.535	3710±1725	10.5	/	/	/	/	/	/

Example 5: Assay for hERG Activity

Cell line: hERG-HEK293

Reagent information

Chemical reagent	Brand
DMEM	Gibco
Fetal bovine serum (FBS)	avantor
G418	GPC
TrypLE™ Express	Gibco
Cisapride	Sigma
K-aspartic	Sigma
Sodium chloride (NaCl)	Sigma
Potassium chloride (KCl)	Sigma
Ethylene glycol bis(2-aminoethyl ether)tetraacetic acid (EGTA)	Sigma
4-Hydroxyethyl piperazine ethanesulfonic acid (HEPES)	Santa Cruz
Magnesium chloride ($MgCl_2$•$6H_2O$)	Sigma
D-glucose	Sigma
Calcium chloride ($CaCl_2$•$2H_2O$)	Sigma
Sodium dihydrogen phosphate (NaH_2PO_4•$2H_2O$)	GENERAL-REAGENT
Adenosine triphosphate sodium salt (Na_2-ATP)	Sigma
Phosphate buffered saline (PBS)	TaKaRa

Patch clamp system instrument and software

Name	Brand	Model
Patch clamp amplifier	HAKA (Germany)	EPC-10
Data acquisition software	HAKA (Germany)	Sutter Patch
Micromanipulator	Sutter Instrument (USA)	MP-285A
Micropipette puller	Sutter Instrument (USA)	P-97
Glass capillary	Sutter Instrument (USA)	BF150-86-10
Inverted microscope	Mshot (China)	MF53-N
Peristaltic pump	LEADFLUID (China)	BT1035
Perfusion system	MappingLab (UK)	MVC-801

Fluids used for recording

Extracellular fluid: 140 mM NaCl, 3.5 mM KCl, 1 mM $MgCl_2$•$6H_2O$, 2 mM $CaCl_2$•$2H_2O$, 10 mM D-glucose, 10 mM HEPES, and 1.25 mM NaH_2PO_4•$2H_2O$; adjusted to pH 7.4 with NaOH.

Cell culture

An HEK-293 cell line stably expressing the hERG potassium channel was used. The hERG potassium channel cells were purchased from Creacell (Cat. No. A-0320).

1) A HEK-293 cell line stably expressing the hERG potassium channel was cultured at 37 °C with 5% carbon dioxide in DMEM medium containing 10% fetal bovine serum and 0.8 mg/mL G418.

2) Cell passage: the old medium was removed, and the cells were washed once with PBS; 1 mL of TrypLE™ Express solution was then added, and the cells were incubated at 37 °C for about 0.5 min. When the cells were detached from the bottom of the dish, about 5 mL of complete culture medium pre-heated at 37 °C was added. The cell suspension was gently pipetted to separate the aggregated cells. The cell suspension was transferred to a sterile centrifuge tube and centrifuged at 1000 rpm for 5 min to collect the cells. The cells were seeded in 6-cm cell culture dishes at a seeded cell amount of 2.5×10^5 cells/dish (final volume: 5 mL) for expansion or maintenance culture.

3) In order to maintain the electrophysiological activity of the cells, the cell density must not exceed 80%.

4) Before patch clamp testing, cells were dissociated with TrypLE™ Express, and 4×10^3 cells were applied to a coverslip and cultured in a 24-well plate (final volume: 500 μL). After 18 h, testing was performed.

Patch clamp testing

The voltage stimulation protocol for whole-cell patch clamp recording of hERG potassium currents was as follows: Once a whole-cell seal was formed, the cell membrane voltage was clamped at -80 mV. The clamping voltage was depolarized from -80 mV to -50 mV for 0.5 s (as leak current detection), then stepped to 30 mV for 2.5 s, and rapidly returned to -50 mV for 4 s to elicit a tail current of the hERG channel. The data were collected repeatedly every 10 s to observe the effect of the drug on the hERG tail current. The 0.5 s, -50 mV stimulation was used as leak current detection. The test data were collected by EPC-10 amplifier (Sutter Instrument) and stored in the Sutter Patch software.

The patch clamp operation was performed as follows: Firstly, a capillary glass tube was drawn into a recording electrode with a microelectrode drawing instrument. An electrode filled with the intracellular fluid was mounted on the microelectrode holder. Under an inverted microscope, a microelectrode manipulator was used to immerse the electrode in the extracellular fluid, and the electrode resistance (Rpip) was recorded. The electrode was then slowly brought into contact with the cell surface, and negative pressure was applied to form a GΩ high-resistance seal. At this time, fast capacitance compensation was performed, and the application of negative pressure was continued to break the cell membrane, forming a whole-cell recording mode. Finally, slow capacitance compensation was performed, and experimental parameters such as series resistance (Rs) were recorded. No current leakage compensation was provided.

Administration was started when the hERG current of the whole-cell record was stable. Each drug concentration was maintained for 5 min (or until the current was stable) for action before the next concentration was measured. One or more concentrations were measured for each test compound. The coverslip with cells applied thereon was placed in the recording chamber of the inverted microscope. The test compound working solution and the compound-free extracellular fluid sequentially flowed through the recording chamber from low to high concentrations by gravity perfusion to act on the cells, and meanwhile, liquid displacement was performed using a peristaltic pump during recording. For each cell, the current detected in the compound-free extracellular fluid was used as its own control group. The test was independently repeated twice using at least two cells per concentration. All electrophysiological experiments were performed at room temperature.

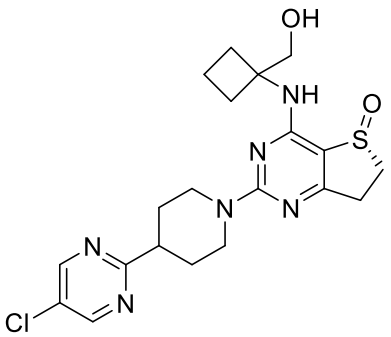
Data analysis

The tail current (*Peak tail current*$_{compound}$) after the action of each drug concentration and the tail current (*Peak tail current*$_{Control}$) of the blank vehicle treatment group were first normalized (*Peak tail current*$_{compound}$/*Peak tail current*$_{Control}$), and then the inhibition rate corresponding to each drug concentration (1-(*Peak tail current*$_{compound}$/*Peak tail current*$_{Control}$) was calculated. Moreover, the mean, standard deviation (SD), and standard error (SE) were calculated for the inhibition rate corresponding to each concentration. The data were expressed as Mean ± SE and saved in Excel. Y = 1/(1 + 10^((LogIC$_{50}$ - X) × HillSlope)). The IC$_{50}$ value of each compound was calculated using the above equation, and non-linear fitting was performed on the concentration-response curve, where IC$_{50}$ represents the half maximal inhibitory concentration. IC$_{50}$ calculation and curve fitting were performed using the GraphPad Prism software.

Experimental results

Compound	Inhibition rate%-10μ (Mean ± SE)
BI1015550	21.00%±0.94%
MX02058	2.03%±2.13%
MX02373	3.68%±3.91%
MX02473	6.58%±0.12%
MX02618	0.75%±1.75%

The structure of compound BI1015550 as a control is shown in the following formula:

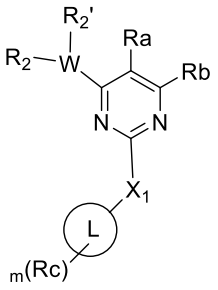


The above experimental results show that the compounds of the present disclosure have a lower potential risk of cardiotoxicity as compared to BI1015550.

The exemplary embodiments of the present disclosure have been described above. It should be understood that the protection scope of the present application is not limited to the illustrative embodiments described above. Any modification, equivalent replacement and improvement and the like made by those skilled in the art without departing from the spirit and principle of the present disclosure shall fall within the scope of protection of the present application.

CLAIMS

1. A compound represented by formula H below, or a racemate, a stereoisomer, a tautomer, an isotopically labeled compound, a solvate, a polymorph, a metabolite, a pharmaceutically acceptable salt, or a prodrug thereof:



H

wherein:

X_1 represents a chemical bond, C_{1-20} alkylene, O, S, NR_q, S(=O), $S(=O)_2$, or C(=O);

R_q is selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, C_{1-8} heteroalkyl-fused C_{6-20} aryl-, C_{1-8} heteroalkyl-C_{6-20} aryl-, NH_2, $-C(O)R_{41}$, $-C(O)OR_{42}$, $-OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

L represents a chemical bond, C_{2-20} alkynyl, or Cy, wherein L may be linked to X_1 or R_c at any position;

Cy represents 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl, wherein the 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl may be optionally fused to 4- to 7-membered cycloalkyl, provided that when the heterocyclyl contains an N atom, the heterocyclyl may be bonded to the carbon atom at the 2-position of the pyrimidine ring in formula H via the N atom or a C atom thereof;

W represents a chemical bond, CH, O, S, N, -S(O)-, $-S(O)_2-$, -C(O), C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene;

R_2 is absent or selected from H and the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d1}: C_{6-20} aryl and 5- to 20-membered heteroaryl;

$R_{2'}$ is absence or represents H, halogen, OH, CN, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d2}: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, and NH_2;

provided that R_2 and $R_{2'}$ are not both "absent";

or alternatively, R_2 and $R_{2'}$, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d3}: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and 6- to 20-membered aryl;

R_a represents H or -X-R_3;

X represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_3 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d4}: C_{1-20} alkyl, -$C(O)R_{61}$, -$C(O)OR_{62}$, -$OC(O)R_{63}$, and NH_2;

R_b represents H or -Y-R_4;

Y represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_4 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d5}: C_{1-20} alkyl, -$C(O)R_{61}$, -$C(O)OR_{62}$, -$OC(O)R_{63}$, and NH_2;

provided that R_a and R_b are not both H;

or R_a and R_b, together with the atoms linked thereto, form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d6}: C_{5-20} cycloalkenyl, 3- to 20-membered heterocyclyl, 5- to 20-membered heteroaryl, and 6- to 20-membered aryl;

R_{d1}, R_{d2}, R_{d3}, R_{d4}, R_{d5}, and R_{d6} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), SO, SO_2, and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20}

alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{31}$, $-CH_2-C(O)R_{31}$, $-C(O)OR_{32}$, $-CH_2C(O)OR_{32}$, $-C(O)NHR_{32}$, $-CH_2C(O)NHR_{32}$, $-OC(O)R_{33}$, $-S(O)_2R_{34}$, $-S(O)_2OR_{35}$, $-OS(O)_2R_{36}$, and $-P(O)(OR_{37})(OR_{38})$;

or when two or more substituents selected from R_{d1}, R_{d2}, R_{d3}, R_{d4}, R_{d5}, and R_{d6} are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_c are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl-O-C_{6-20} aryl-, 5- to 20-membered heteroaryl-N-C_{6-20} aryl-, 5- to 20-membered heteroaryl-S-C_{6-20} aryl-, 5- to 20-membered heteroaryl-CH_2-C_{6-20} aryl-, C_{4-10} cycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-fused C_{6-20} aryl-, C_{4-10} cycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl, C_{4-10} cycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-fused 5- to 20-membered heteroaryl-, C_{4-10} cycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-5- to 20-membered heteroaryl-, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{31}$, $-C(O)OR_{32}$, $-OC(O)R_{33}$, $-S(O)_2R_{34}$, $-S(O)_2OR_{35}$, $-OS(O)_2R_{36}$, and $-P(O)(OR_{37})(OR_{38})$;

m is selected from integers from 1 to 10;

R_e are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, NH_2, oxo (=O), thio (=S), O-$CONH_2$, O-$CONHR_f$, and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy,

C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, C_{1-8} heteroalkyl-fused C_{6-20} aryl-, C_{1-8} heteroalkyl-C_{6-20} aryl-, NH_2, $-C(O)R_{41}$, $-C(O)OR_{42}$, $-OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

or when two or more substituents selected from R_e are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_f are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{51}$, $-C(O)OR_{52}$, $-OC(O)R_{53}$, $-S(O)_2R_{54}$, $-S(O)_2OR_{55}$, $-OS(O)_2R_{56}$, and $-P(O)(OR_{57})(OR_{58})$;

or when two or more substituents selected from R_f are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_g are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, and R_{58} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3-

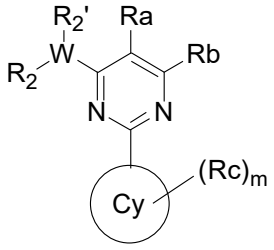
to 20-membered heterocyclyl, and NH_2;

the 3- to 20-membered heterocyclyl represents a saturated or unsaturated non-aromatic ring or ring system; for example, it is a 4-, 5-, 6-, or 7-membered monocyclic ring system, a 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic (e.g., fused, bridged, or spiro) ring system, or a 10-, 11-, 12-, 13-, 14-, or 15-membered tricyclic ring system, and contains at least one, e.g., 1, 2, 3, 4, 5, or more heteroatoms independently selected from O, S, and N, wherein N and S may also be optionally oxidized to various oxidized forms to form nitrogen oxides, -S(O)-, or $-S(O)_2-$;

the C_{6-20} aryl represents an aromatic or partially aromatic monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic hydrocarbon ring having 6-20 carbon atoms, which may be a single aromatic ring or multiple aromatic rings fused together;

the 5- to 20-membered heteroaryl represents a monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic aromatic ring system, wherein the aromatic ring system has 5-20 ring atoms and contains 1, 2, 3, 4, 5, or more heteroatoms independently selected from N, O, and S;

for example, a compound represented by formula G below, or a racemate, a stereoisomer, a tautomer, an isotopically labeled compound, a solvate, a polymorph, a metabolite, a pharmaceutically acceptable salt, or a prodrug thereof:



G

wherein:

Cy represents a chemical bond, 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl, provided that when the heterocyclyl contains an N atom, the heterocyclyl may be bonded to the carbon atom at the 2-position of the pyrimidine ring in formula G via the N atom or a C atom thereof;

W represents a chemical bond, CH, O, S, N, -S(O)-, $-S(O)_2-$, -C(O), C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene;

R_2 is absent or selected from H and the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d1}: C_{6-20} aryl and 5- to 20-membered heteroaryl;

$R_{2'}$ is absence or represents H, halogen, OH, CN, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d2}: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20}

cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, and NH_2;

provided that R_2 and $R_{2'}$ are not both "absent";

or alternatively, R_2 and $R_{2'}$, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d3}: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and 6- to 20-membered aryl;

R_a represents H or -X-R_3;

X represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_3 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d4}: C_{1-20} alkyl, -$C(O)R_{61}$, -$C(O)OR_{62}$, -$OC(O)R_{63}$, and NH_2;

R_b represents H or -Y-R_4;

Y represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_4 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d5}: C_{1-20} alkyl, -$C(O)R_{61}$, -$C(O)OR_{62}$, -$OC(O)R_{63}$, and NH_2;

provided that R_a and R_b are not both H;

or R_a and R_b, together with the atoms linked thereto, form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d6}: C_{5-20} cycloalkenyl, 3- to 20-membered heterocyclyl, 5- to 20-membered heteroaryl, and 6- to 20-membered aryl;

R_{d1}, R_{d2}, R_{d3}, R_{d4}, R_{d5}, and R_{d6} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, -

$C(O)R_{31}$, $-CH_2-C(O)R_{31}$, $-C(O)OR_{32}$, $-CH_2C(O)OR_{32}$, $-C(O)NHR_{32}$, $-CH2C(O)NHR_{32}$, $-OC(O)R_{33}$, $-S(O)_2R_{34}$, $-S(O)_2OR_{35}$, $-OS(O)_2R_{36}$, and $-P(O)(OR_{37})(OR_{38})$;

or when two or more substituents selected from R_{d1}, R_{d2}, R_{d3}, R_{d4}, R_{d5}, and R_{d6} are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_c are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{31}$, $-C(O)OR_{32}$, $-OC(O)R_{33}$, $-S(O)_2R_{34}$, $-S(O)_2OR_{35}$, $-OS(O)_2R_{36}$, and $-P(O)(OR_{37})(OR_{38})$;

m is selected from integers from 1 to 10;

R_e are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{41}$, $-C(O)OR_{42}$, $-OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

or when two or more substituents selected from R_e are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_f are identical or different, and are each independently selected from H, halogen, OH, CN,

NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{51}$, $-C(O)OR_{52}$, $-OC(O)R_{53}$, $-S(O)_2R_{54}$, $-S(O)_2OR_{55}$, $-OS(O)_2R_{56}$, and $-P(O)(OR_{57})(OR_{58})$;

or when two or more substituents selected from R_f are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_g are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, and R_{58} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

the 3- to 20-membered heterocyclyl represents a saturated or unsaturated non-aromatic ring or ring system; for example, it is a 4-, 5-, 6-, or 7-membered monocyclic ring system, a 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic (e.g., fused, bridged, or spiro) ring system, or a 10-, 11-, 12-, 13-, 14-, or 15-membered tricyclic ring system, and contains at least one, e.g., 1, 2, 3, 4, 5, or more heteroatoms independently selected from O, S, and N, wherein N and S may also be optionally oxidized to various oxidized forms to form nitrogen oxides, -S(O)-, or $-S(O)_2-$;

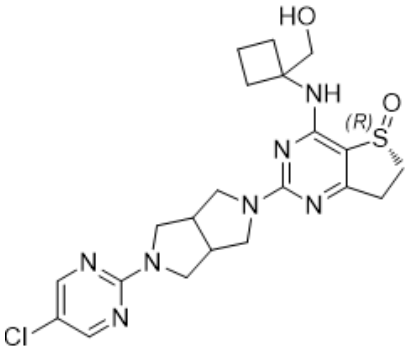
the C_{6-20} aryl represents an aromatic or partially aromatic monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic hydrocarbon ring having 6-20 carbon atoms, which may be a single aromatic ring or multiple aromatic rings fused together;

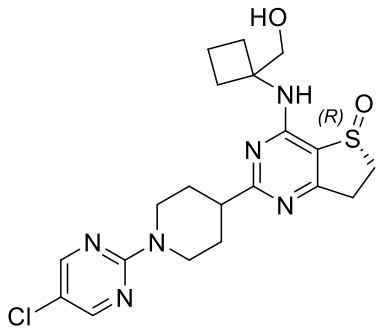
the 5- to 20-membered heteroaryl represents a monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic aromatic ring system, wherein the aromatic ring system has 5-20

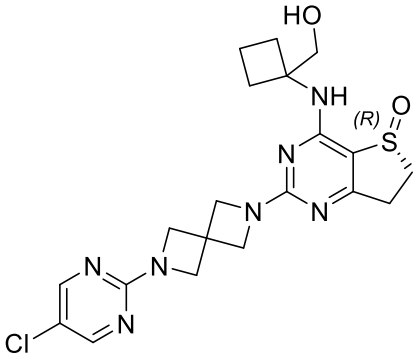
ring atoms and contains 1, 2, 3, 4, 5, or more heteroatoms independently selected from N, O, and S;

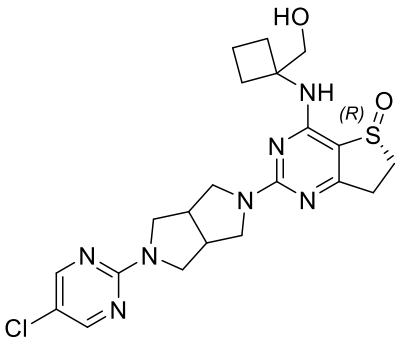
preferably, the cycloalkyl may be saturated or partially saturated;

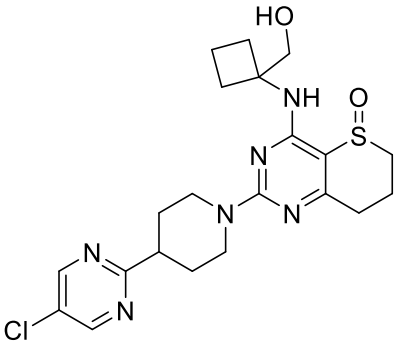
preferably, the compound does not comprise a compound and/or a stereoisomer thereof and/or a racemate thereof selected from:

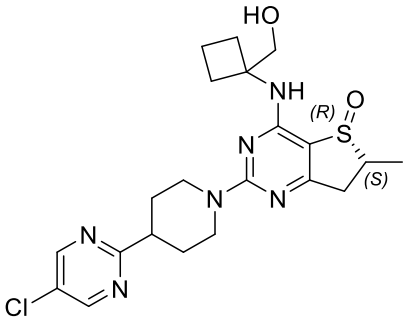


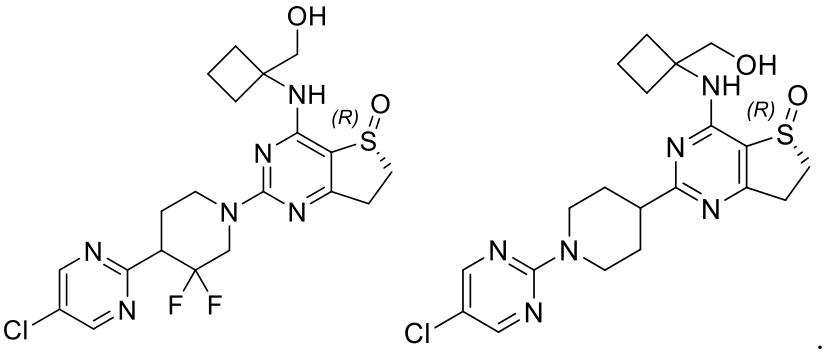




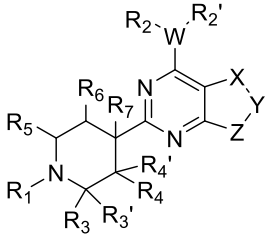




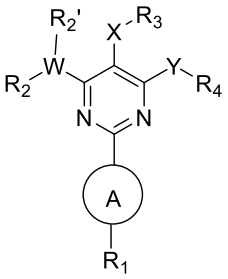




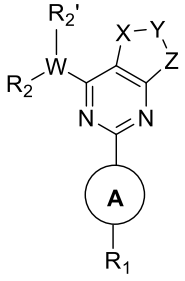
2. The compound represented by formula G, or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 1, wherein the compound represented by formula G is selected from compounds represented by the following formulas I, II, III, IV, V, VI, VII and VIII:



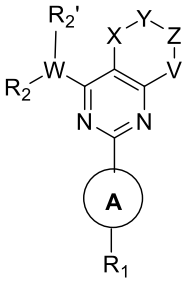
Formula I



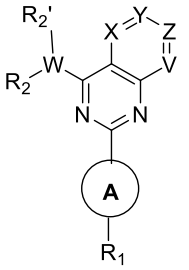
Formula II



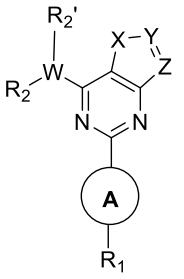
Formula III



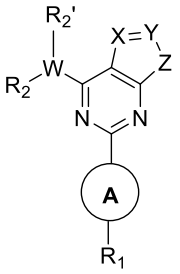
Formula IV



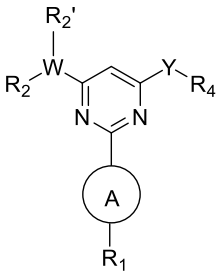
Formula V



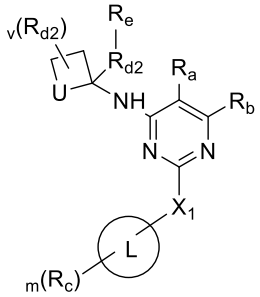
Formula VI



Formula VII

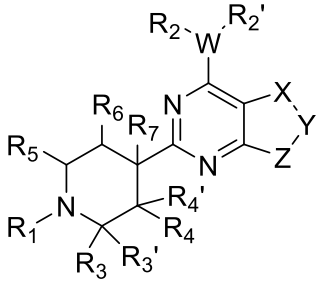


Formula VIII



Formula IX .

3. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula I has the following definitions:



I

wherein:

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20}

aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$; or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be

independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, $SR^{2.1}$, $C_{1\text{-}3}$ alkyl-$SR^{2.1}$, SO-$R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl alcohol, $C_{1\text{-}3}$ haloalkyl, a mono- or bicyclic ring, -$C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-($C_{1\text{-}3}$ alkyl), halogen, $C_{1\text{-}10}$ alkyl, and $C_{6\text{-}20}$ aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from $C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-($C_{1\text{-}3}$ alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $COOR^{2.1}$; or

$R_{2'}$ represents H, F, Me, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $C_{6\text{-}10}$ aryl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, $C_{5\text{-}10}$ heteroaryl-$C_{1\text{-}6}$ alkyl, a $C_{3\text{-}10}$ heterocyclic ring, a $C_{5\text{-}10}$ heterocyclic ring, -NR'R'', fluorine, $C_{1\text{-}6}$ fluoroalkyl, and $C_{1\text{-}6}$ fluoroalkoxy, wherein R' and R'' are independently selected from H and $C_{1\text{-}6}$ alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, $C_{1\text{-}6}$ alkyl, and O-$C_{1\text{-}6}$ alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or

bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

R_3 represents H, C_{1-6} alkyl, F, chlorine, bromine, hydroxyl, -CN, $-CH_2CN$, $-CH_2COOR$, -COOR, -CO-$NH(CH_3)C_{1-3}$ fluoroalkyl, (C_{1-6} alkyl)-OH, (C_{1-6} alkyl)-OCH_3, (C_{1-6} alkyl)-NH_2, (C_{1-6} alkyl)-N(C_{1-3} alkyl), or (C_{1-6} alkyl)-NH;

$R_{3'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-20} aryl, C_{6-20} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more groups selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_3 and $R_{3'}$ together represent oxo, methylene, ethylene, and propylene, which may be optionally substituted with substituents selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and O-(C_{1-3} alkyl);

R_4 represents H, C_{1-6} alkyl, F, chlorine, bromine, hydroxyl, -CN, $-CH_2CN$, $-CH_2COOR$, -COOR, -CO-$NH(CH_3)C_{1-3}$ fluoroalkyl, (C_{1-6} alkyl)-OH, (C_{1-6} alkyl)-OCH_3, (C_{1-6} alkyl)-NH_2, (C_{1-6} alkyl)-N(C_{1-3} alkyl), or (C_{1-6} alkyl)-NH;

$R_{4'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-20} aryl, C_{6-20} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more groups selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_4 and $R_{4'}$ together represent oxo, methylene, ethylene, and propylene, which may be optionally substituted with substituents selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and O-(C_{1-3} alkyl);

R_5 and R_6 independently represent H, F, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-6} alkyl-OH, C_{1-6}

alkenyl-OCH_3, C_{1-6} alkyl-NH_2, C_{1-6} alkynyl-$NH(C_{1-3}$ alkyl), and C_{1-6} alkyl-$N(C_{1-3}$ alkyl$)_2$;

or R_1 and R_3, together with the C- and N-atoms of piperidine, form a saturated or partially saturated 5- or 7-membered heterocyclic group that contains two or three nitrogen atoms, which may be optionally substituted with groups selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

or R_3 and R_6 together form a bridged ring of methylene, ethylene, and propylene, which may be optionally substituted with groups selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

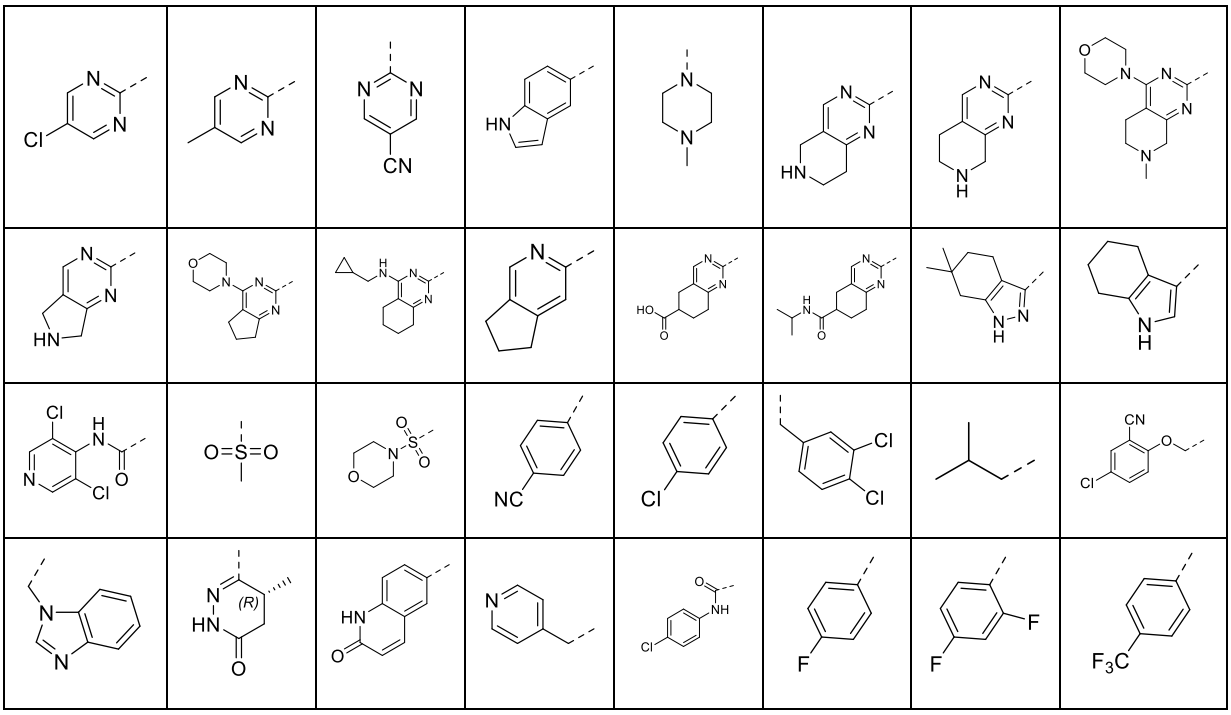
or R_3 and R_5 together form a bridged ring of methylene, ethylene, and propylene, which may be optionally substituted with groups selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

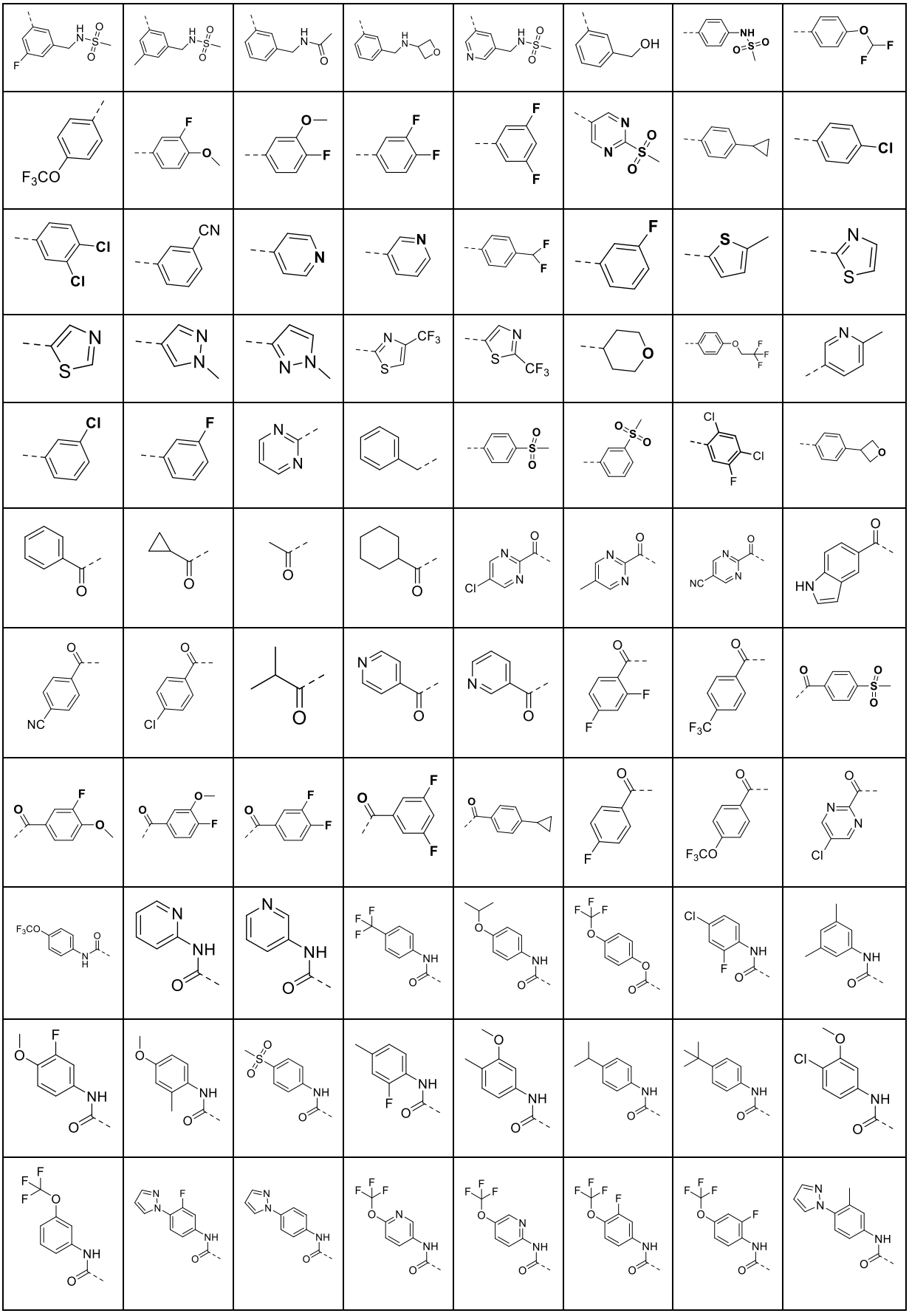
or R_3 and R_4 together form a bridged ring of methylene, ethylene, and propylene, which may be optionally substituted with groups selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

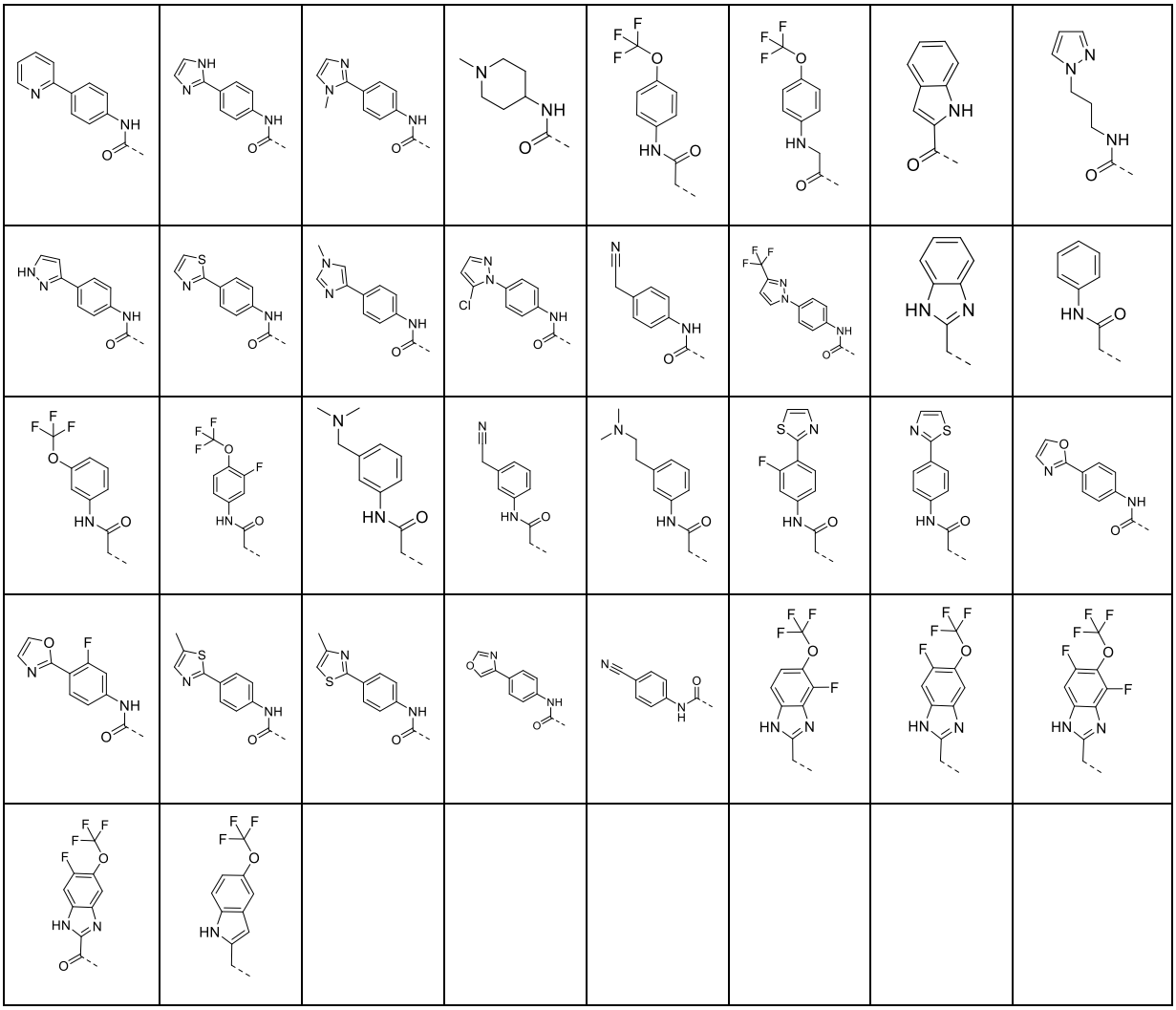
or R_4 and R_6 together form a bridged ring of methylene, ethylene, and propylene, which may be optionally substituted with groups selected from $-CH_3$, -OH, -F, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $O-(C_{1-3}$ alkyl);

or R_4 and R_7, together with the carbon atom linked thereto, form a double bond;

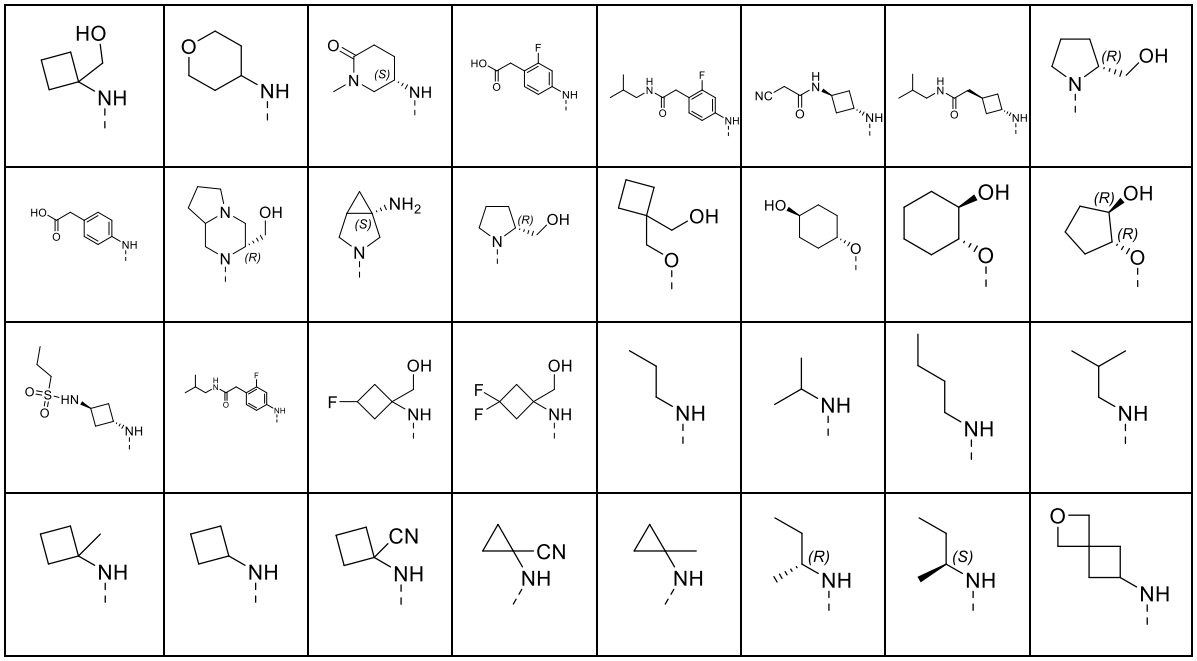
for example, R_1 may be selected from the following groups:

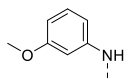
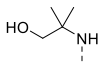
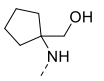
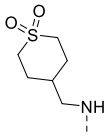
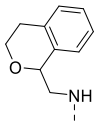
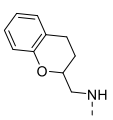
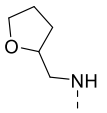
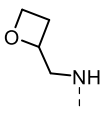
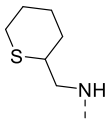
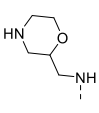
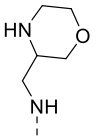
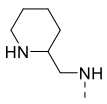
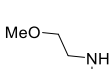
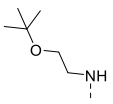
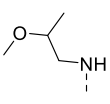
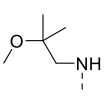
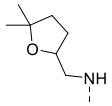
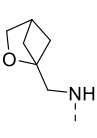
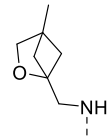
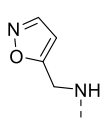
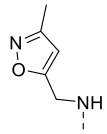
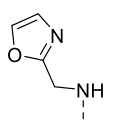
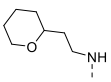
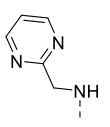
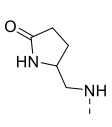
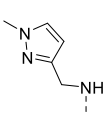
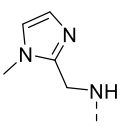
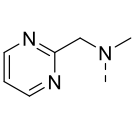
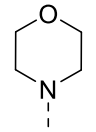
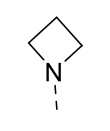
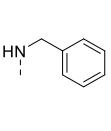
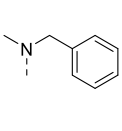
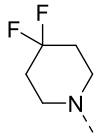
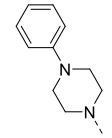


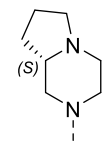
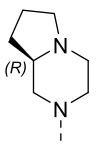
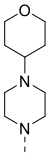
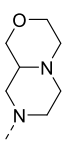
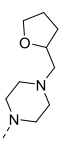
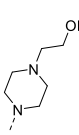
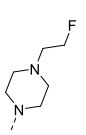
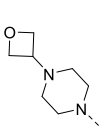
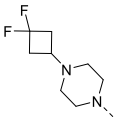
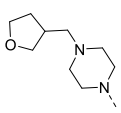
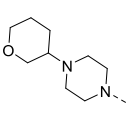
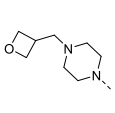
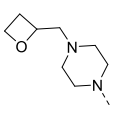
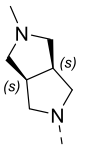
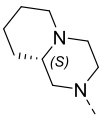
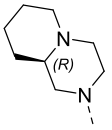
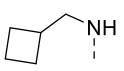
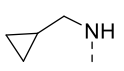
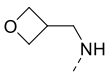
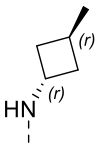
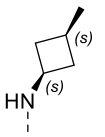
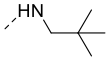
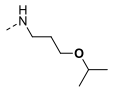
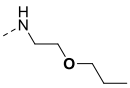
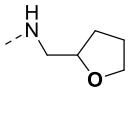
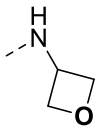
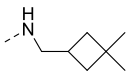
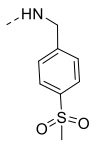
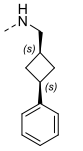
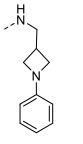
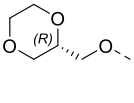
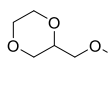
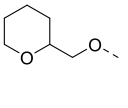
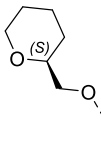
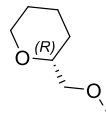
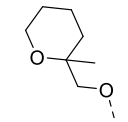
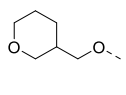
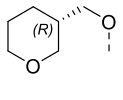
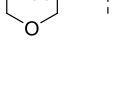
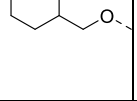


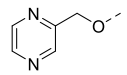
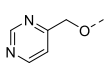
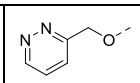
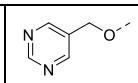
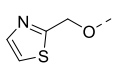
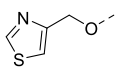
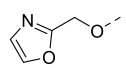
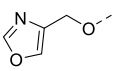
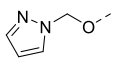
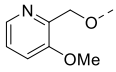
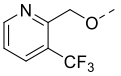
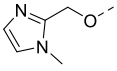
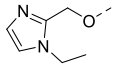
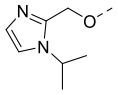
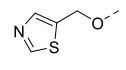
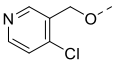
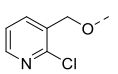
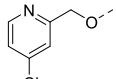
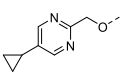
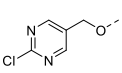
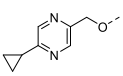
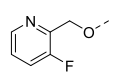
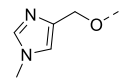
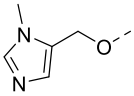
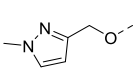
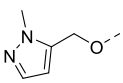
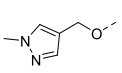
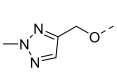
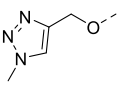
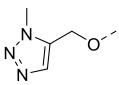
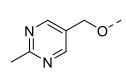
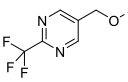
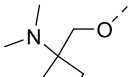
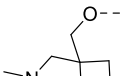
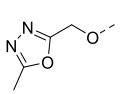
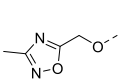
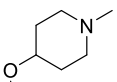
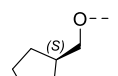
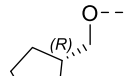
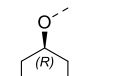


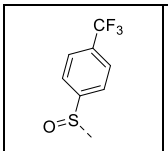
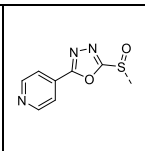
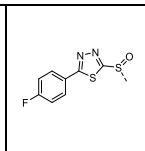
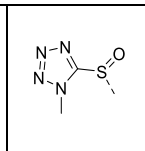
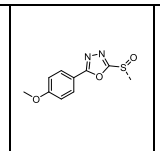
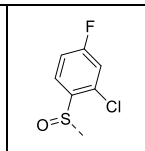
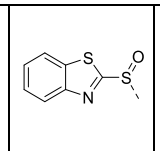
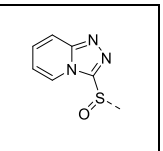
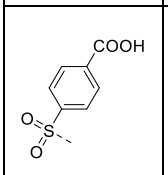
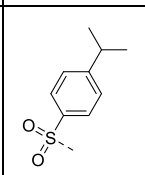
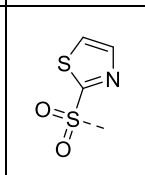
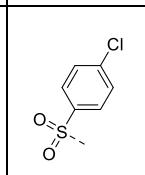
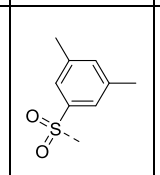
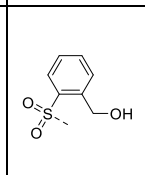
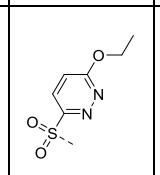
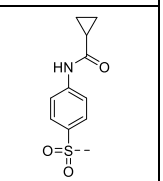
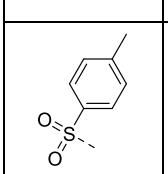
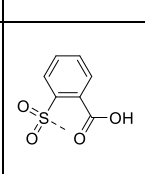
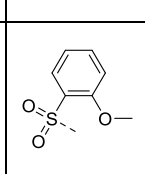
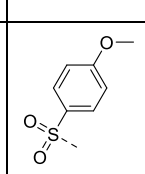
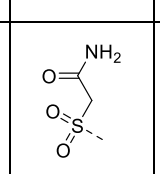
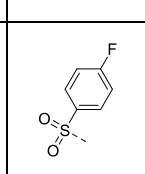
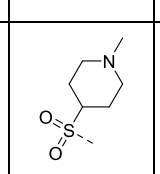
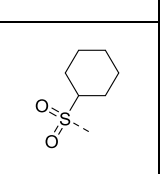
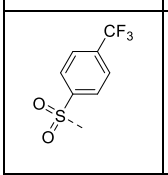
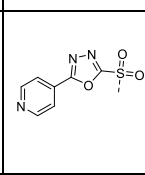
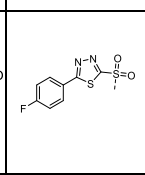
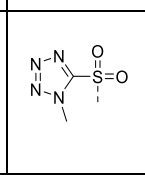
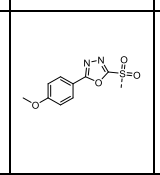
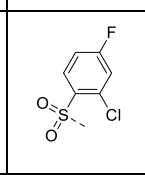
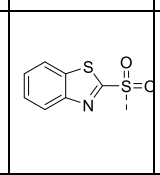
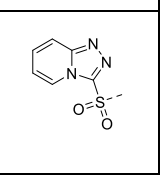
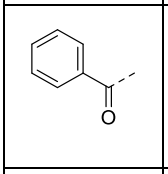
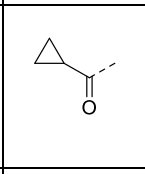
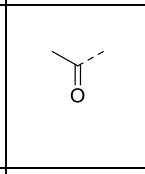
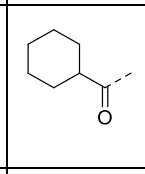
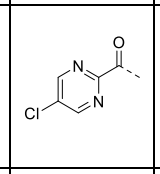
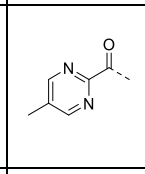
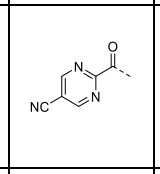
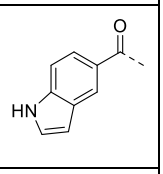
for example, -W-$R_2R_{2'}$ may be selected from the following groups:



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4. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula II has the following definitions:

II

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or

bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{5-10} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents is optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4

heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{5-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-20} aryl, C_{6-20} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or,

R_2 and $R_{2'}$ together form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

R_3 represents a group selected from aryl and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or independently and optionally substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents

may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{2.3}$;

R_4 represents a group selected from aryl and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or independently and optionally substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-

membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

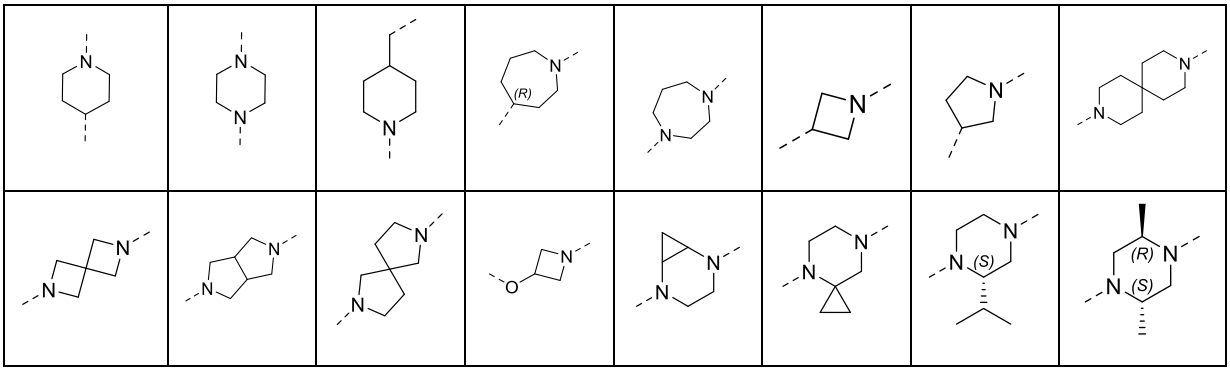
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

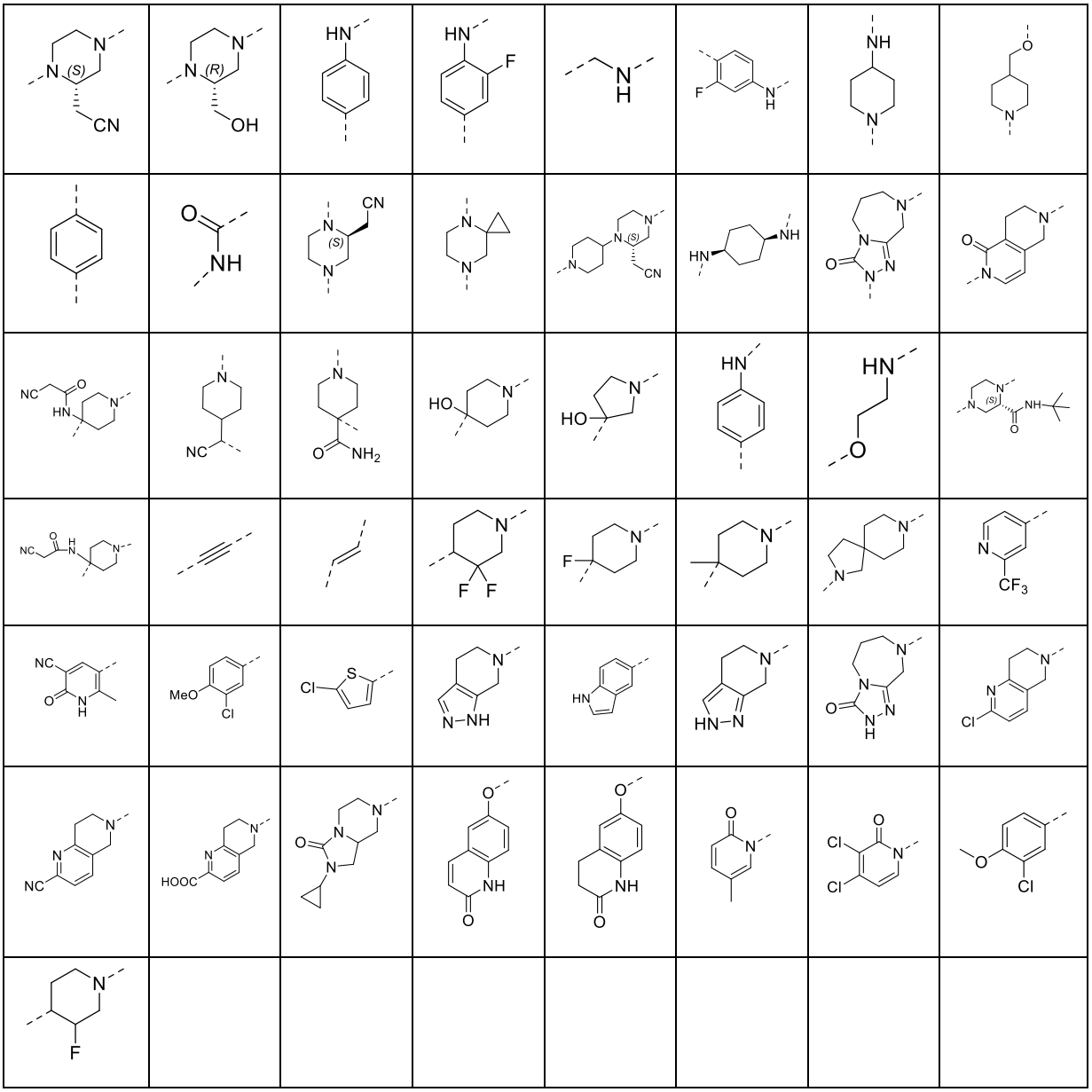
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

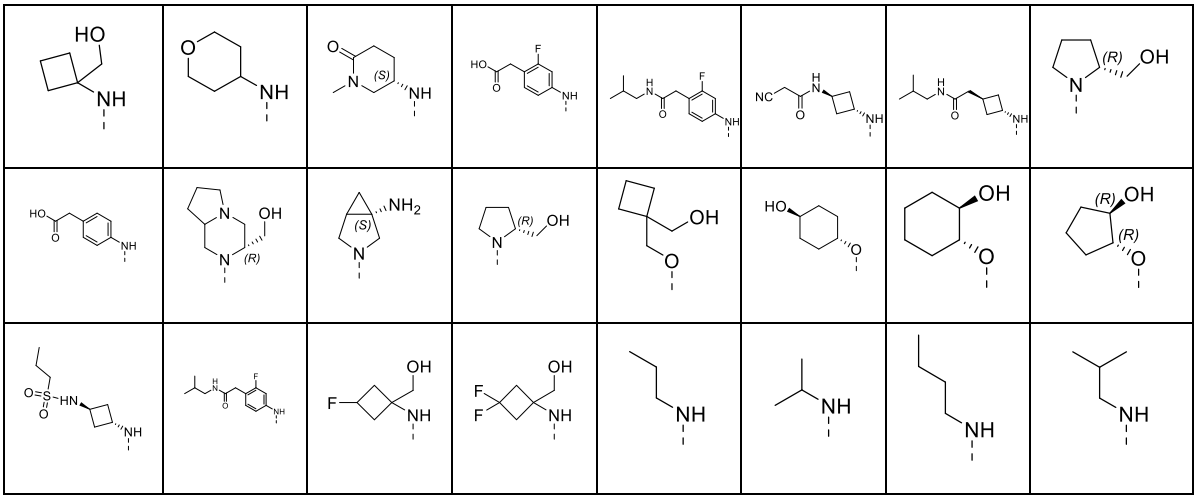
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

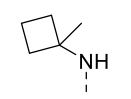
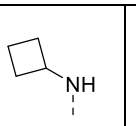
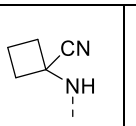
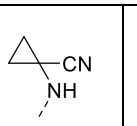
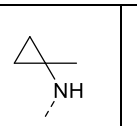
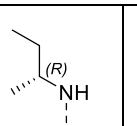
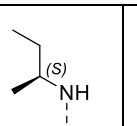
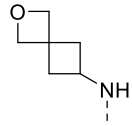
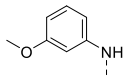
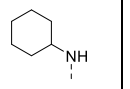
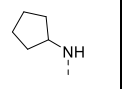
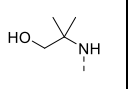
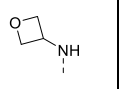
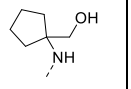
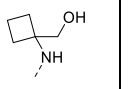
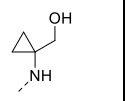
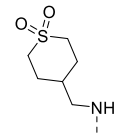
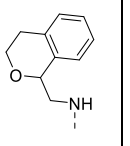
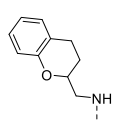
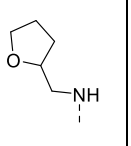
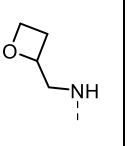
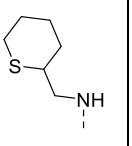
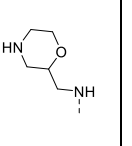
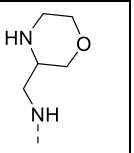
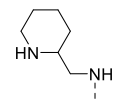
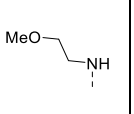
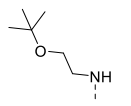
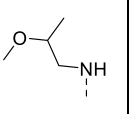
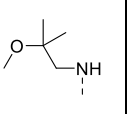
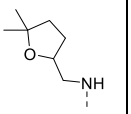
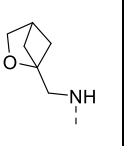
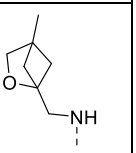
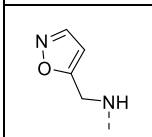
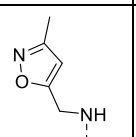
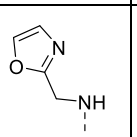
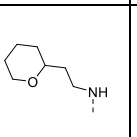
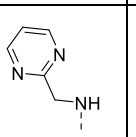
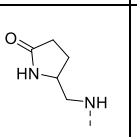
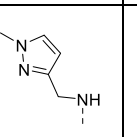
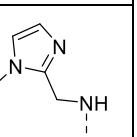
for example, ring A may be selected from the following groups:

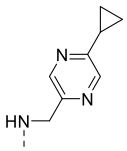
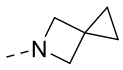
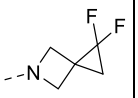
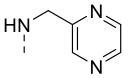
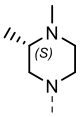
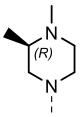
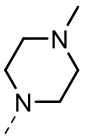
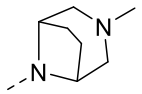
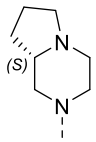
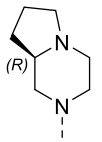
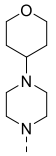
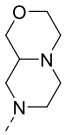
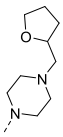
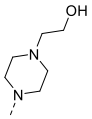
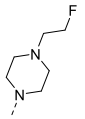
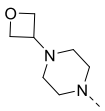
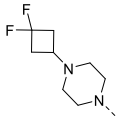
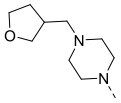
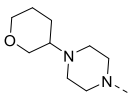
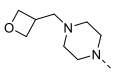
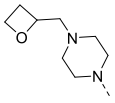
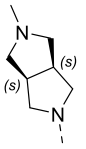
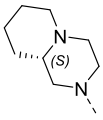
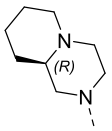
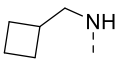
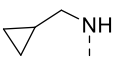
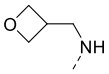
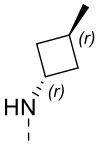
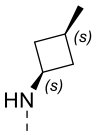
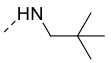
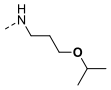
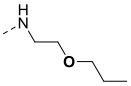
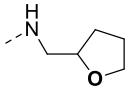
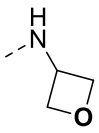
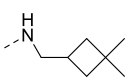
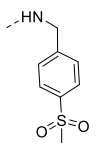
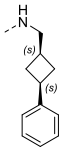
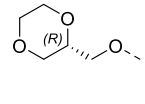
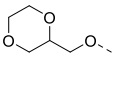


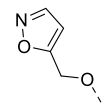
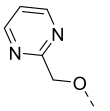
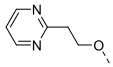
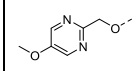
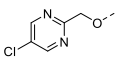
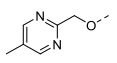
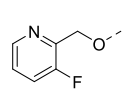
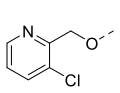
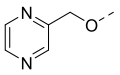
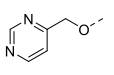
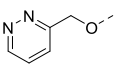
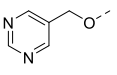
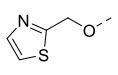
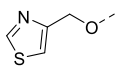
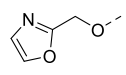
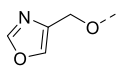
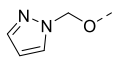
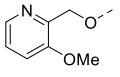
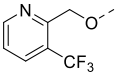
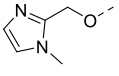
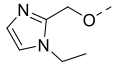
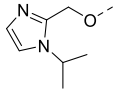
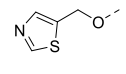
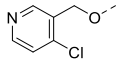
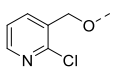
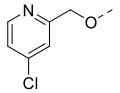
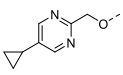
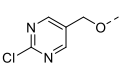
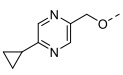
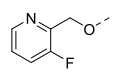
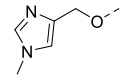
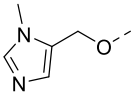
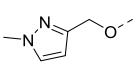
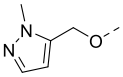
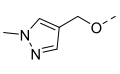
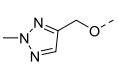
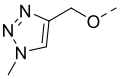
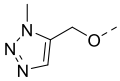
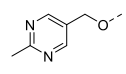
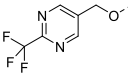


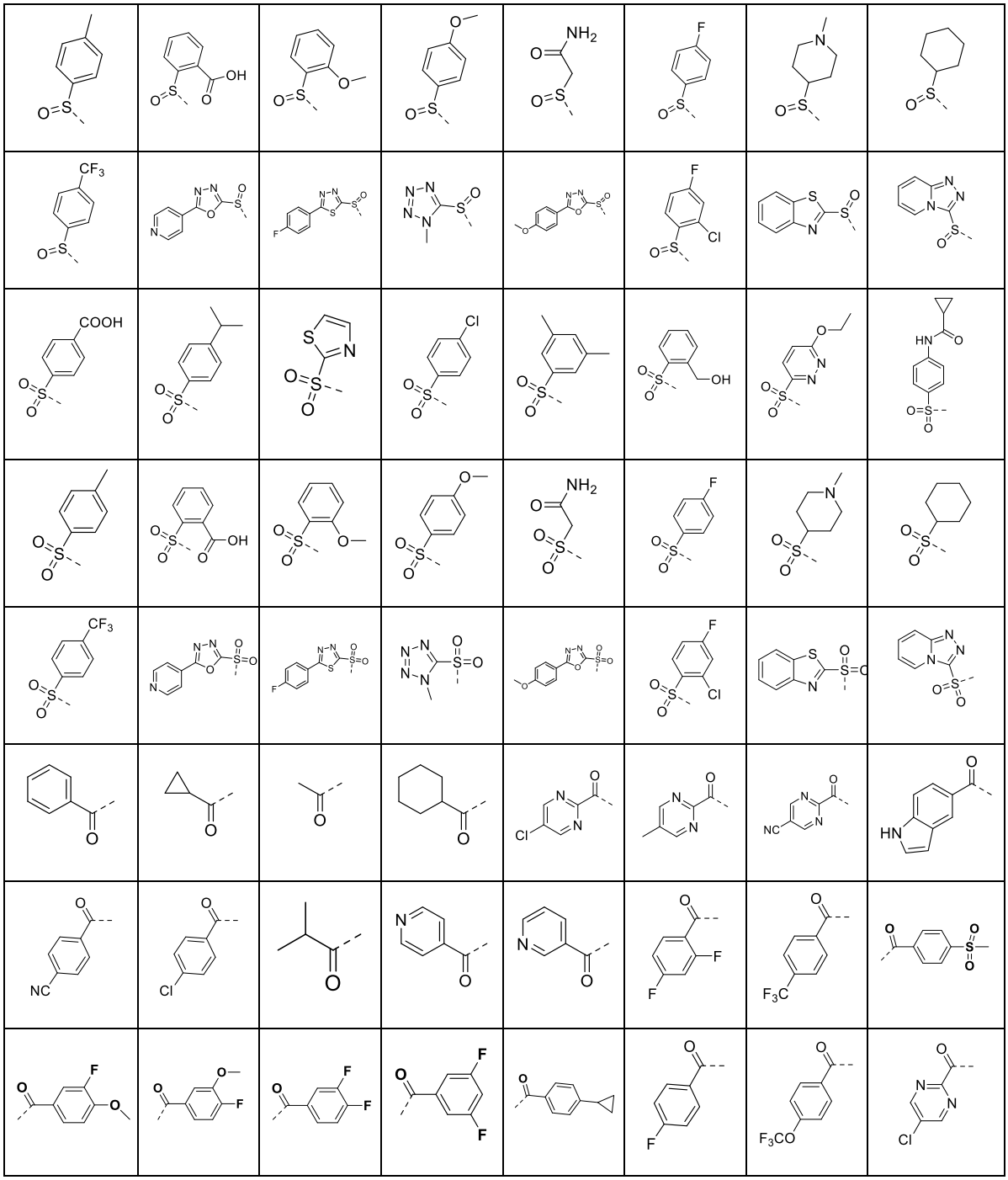
for example, -W-$R_2R_{2'}$ may be selected from the following groups:





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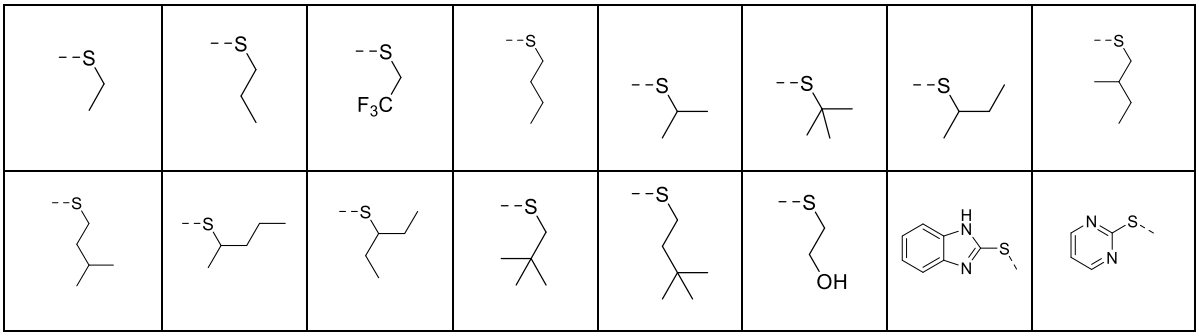

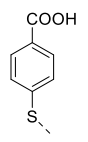	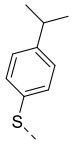	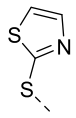	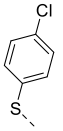	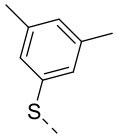	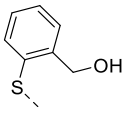	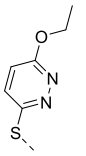	
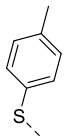	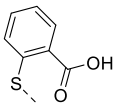	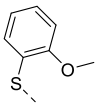	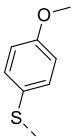	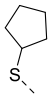	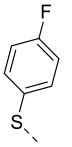	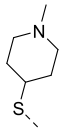	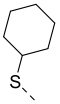
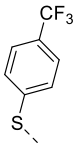	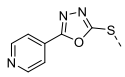	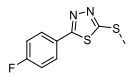		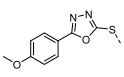	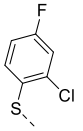	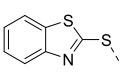	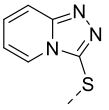
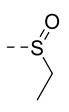	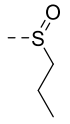	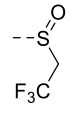		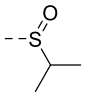	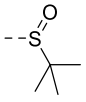	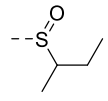	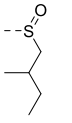
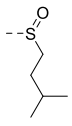	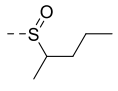	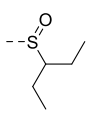	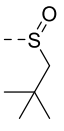	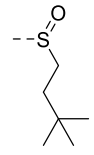	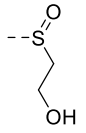	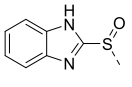	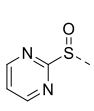

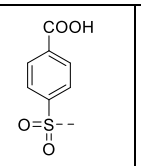	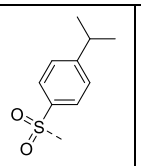	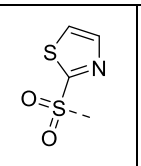	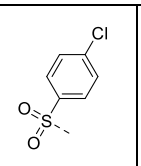	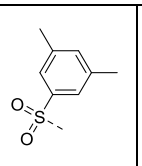	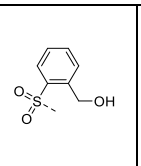	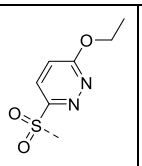	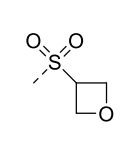
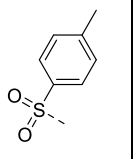	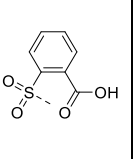	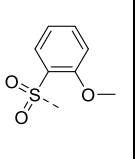	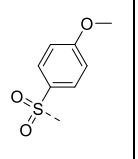	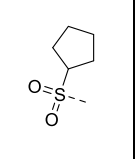	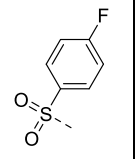	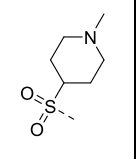	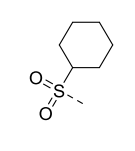
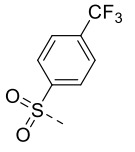	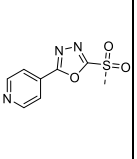	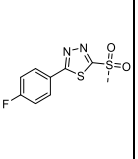	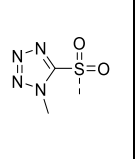	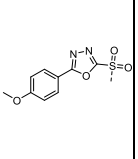	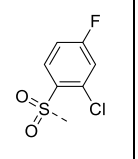	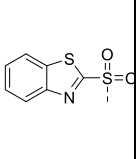	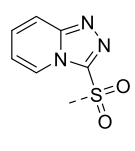

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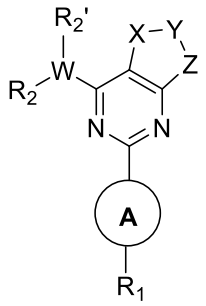
5. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula III has the following definitions:



III

wherein:

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), $C_{1\text{-}2}$ alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic $C_{6\text{-}20}$ aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, $C_{3\text{-}10}$ cycloalkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, $C_{1\text{-}}$

$_6$ alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $NR^{2.2}R^{2.3}$, $CH_2\text{-}NR^{2.2}R^{2.3}$, $CH_2CH_2\text{-}NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, $SO_2\text{-}R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered, monocyclic or bicyclic, optionally related, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally

substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and

optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

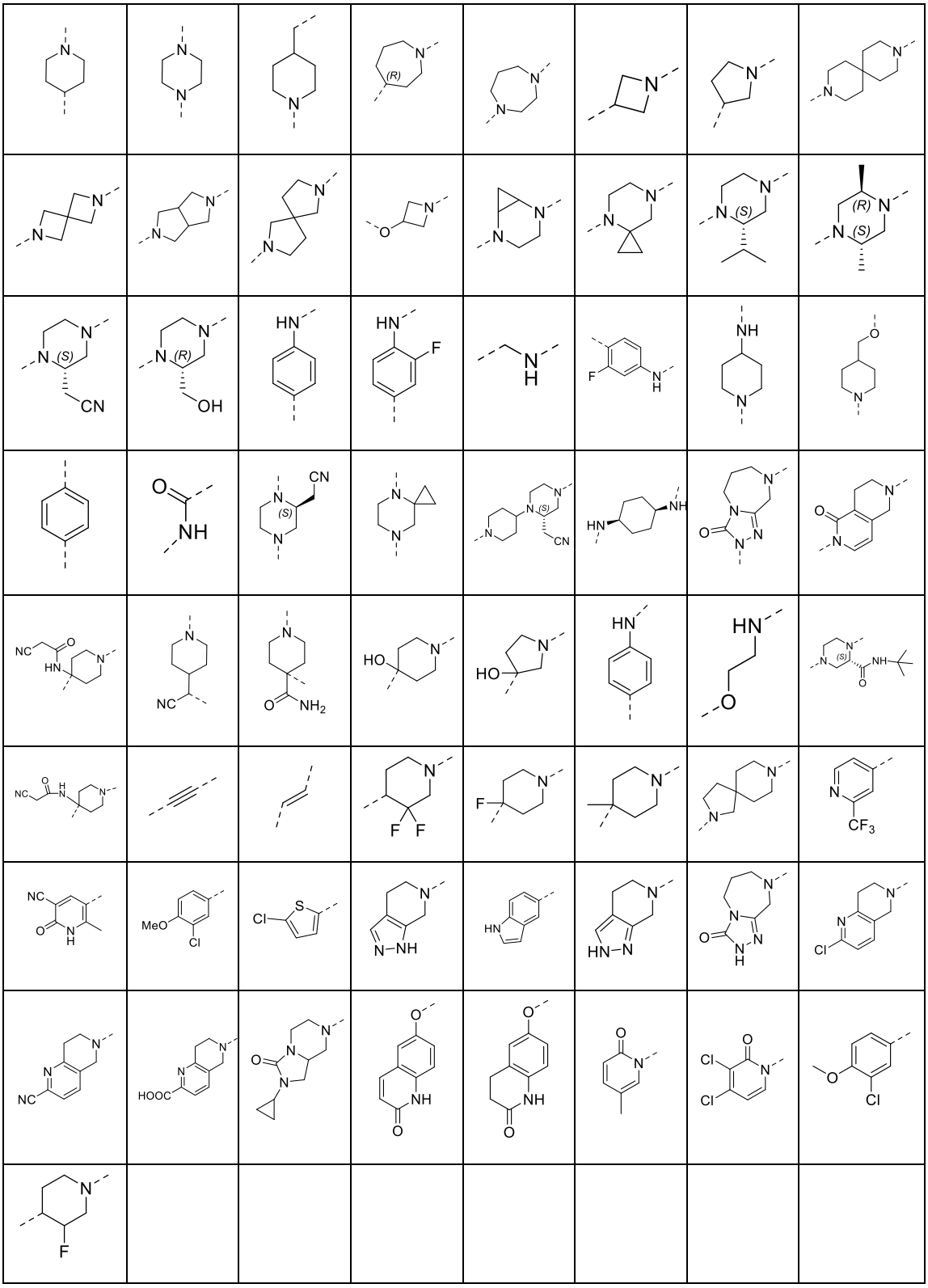
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

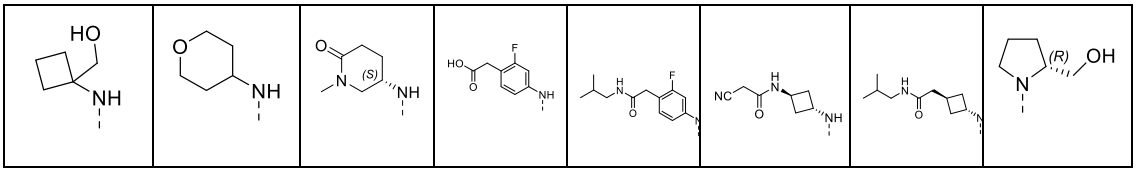
$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

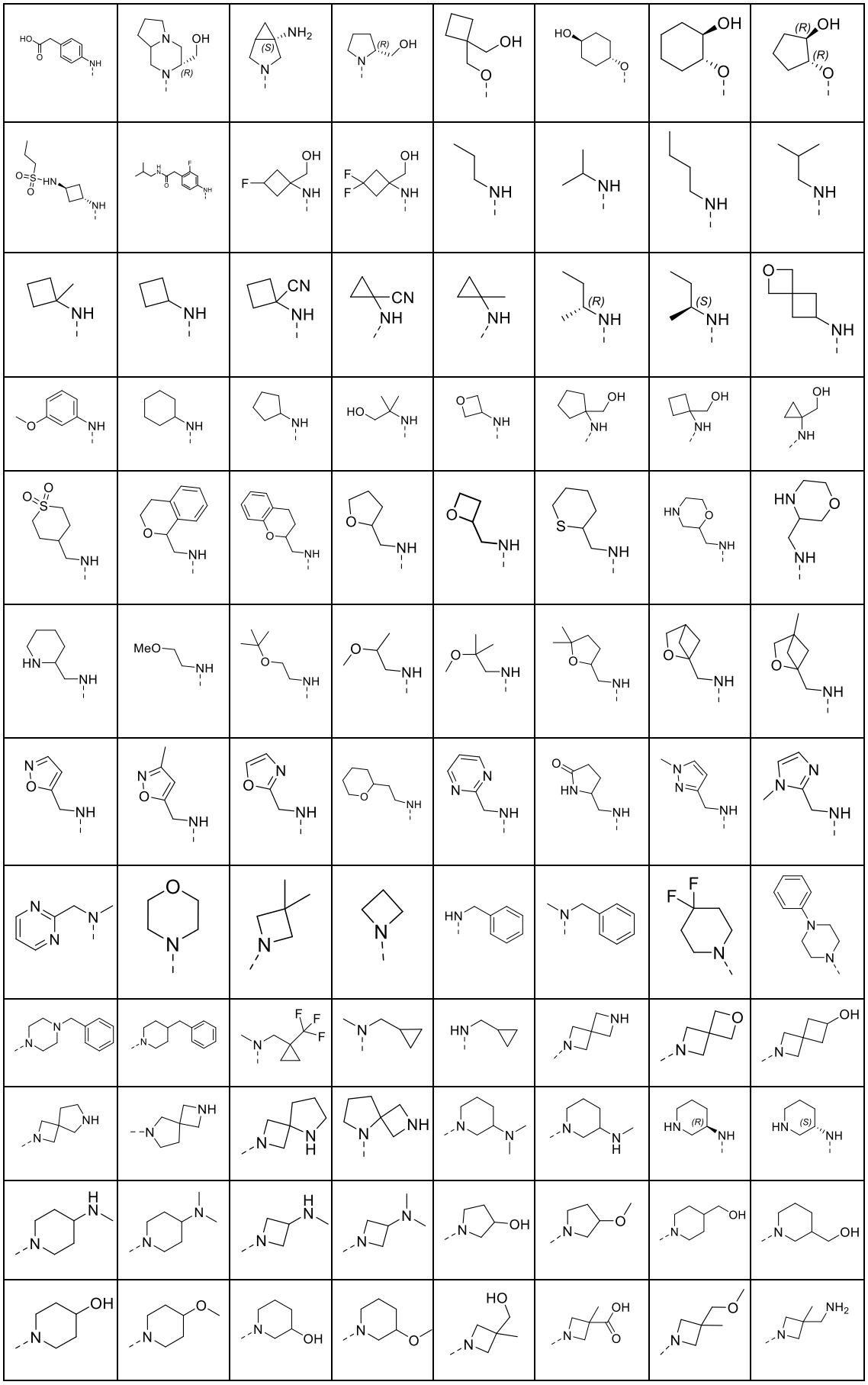
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

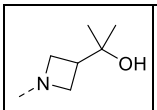
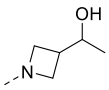
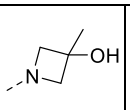
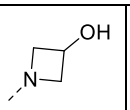
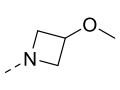
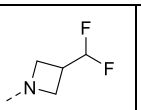
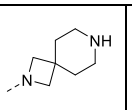
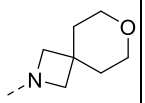
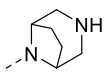
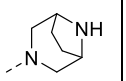
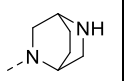
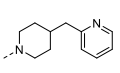
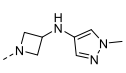
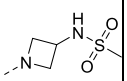
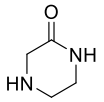
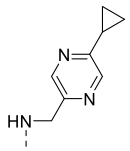
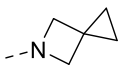
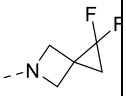
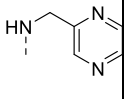
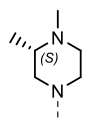
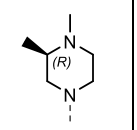
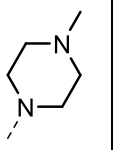
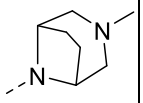
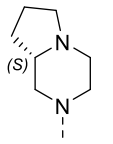
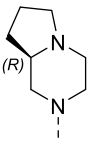
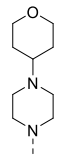
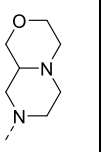
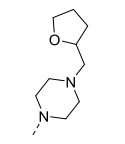
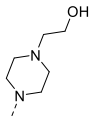
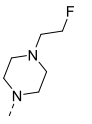
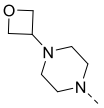
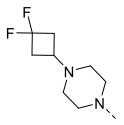
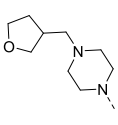
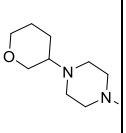
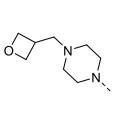
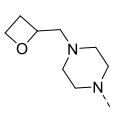
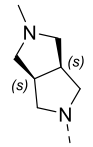
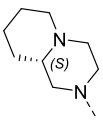
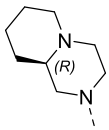
for example, ring A may be selected from the following groups:

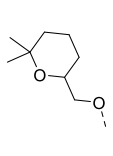
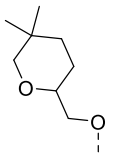
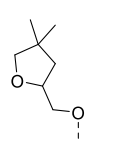
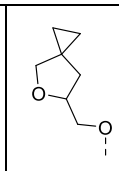
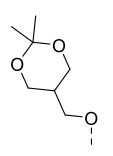
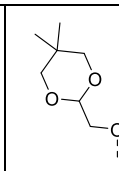
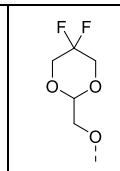
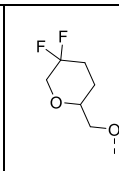
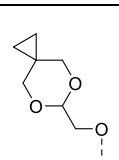
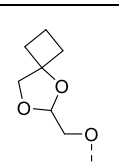
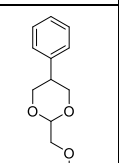
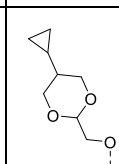
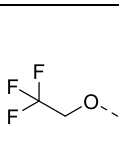
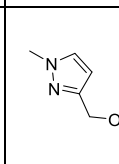
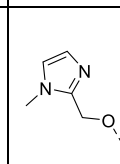
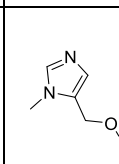
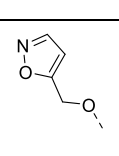
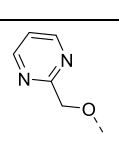
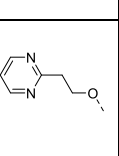
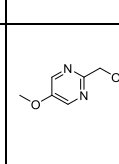
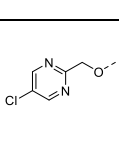
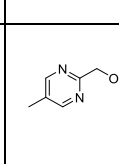
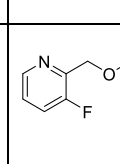
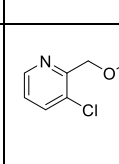
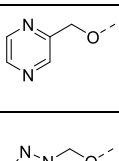
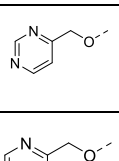
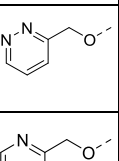
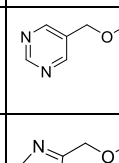
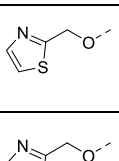
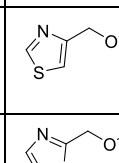
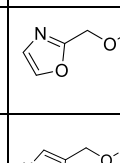
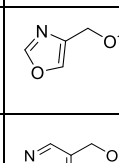
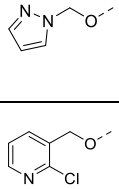
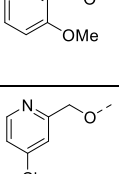
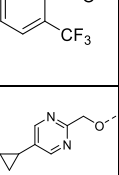
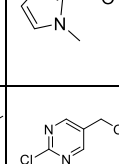
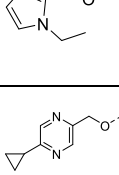
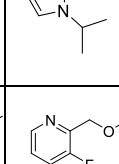
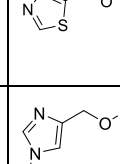
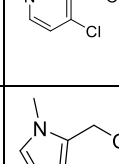


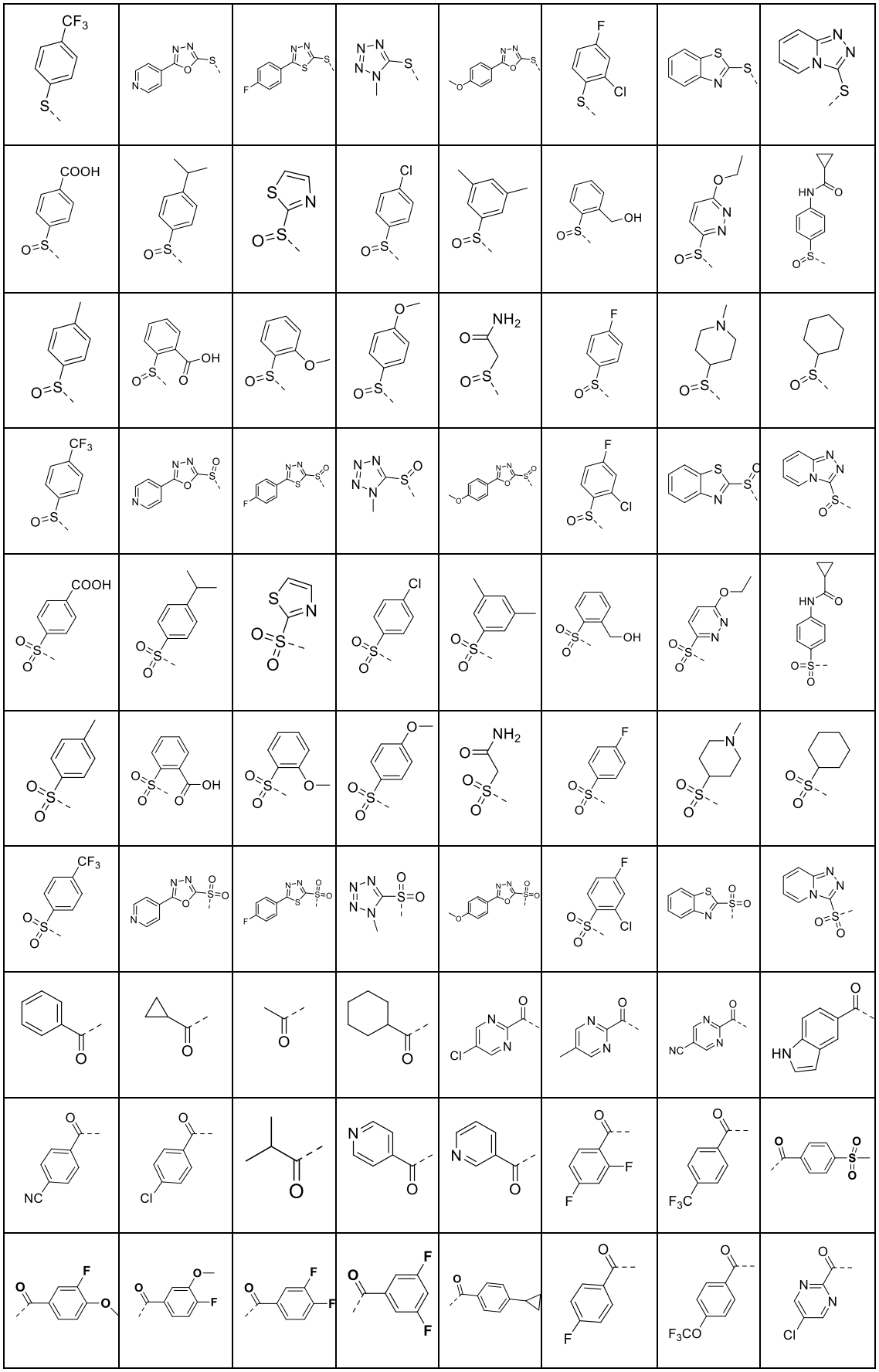
for example, -W-$R_2R_{2'}$ may be selected from the following groups:







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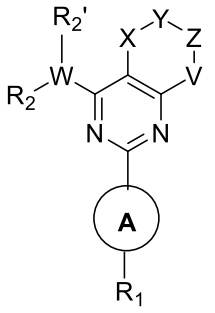
6. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula IV has the following definitions:



IV

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

V represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

or R1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$,

$CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH=CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH=CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, $CO\text{-}NH_2$, $CO\text{-}NH\text{-}CH_3$, $-CO\text{-}N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, $SR^{2.1}$, $C_{1\text{-}3}$ alkyl-$SR^{2.1}$, SO-$R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=$CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, $C_{6\text{-}20}$ aryl, and $NR^{2.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic $C_{6\text{-}20}$ aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=$CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, $C_{3\text{-}10}$ cycloalkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ fluoroalkyl, CF_3, CHF_2, CH_2F, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $C_{1\text{-}3}$ alkyl-$OR^{1.1}$, $SR^{1.1}$, $C_{1\text{-}3}$ alkyl-$SR^{1.1}$, SO-$R^{1.1}$, $C_{1\text{-}3}$ alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=$CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally

substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

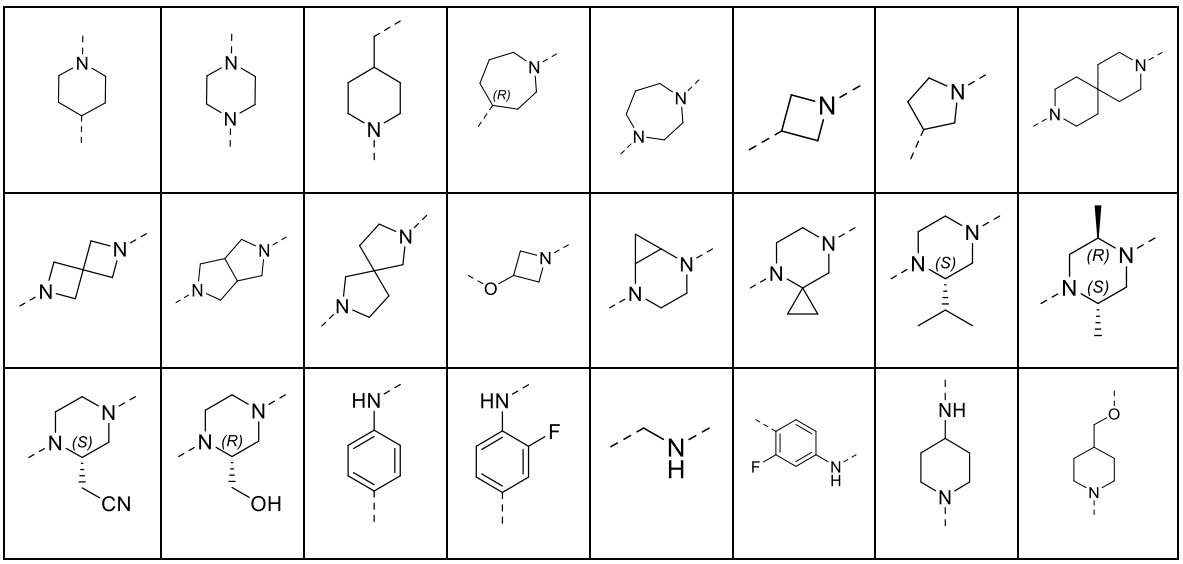
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

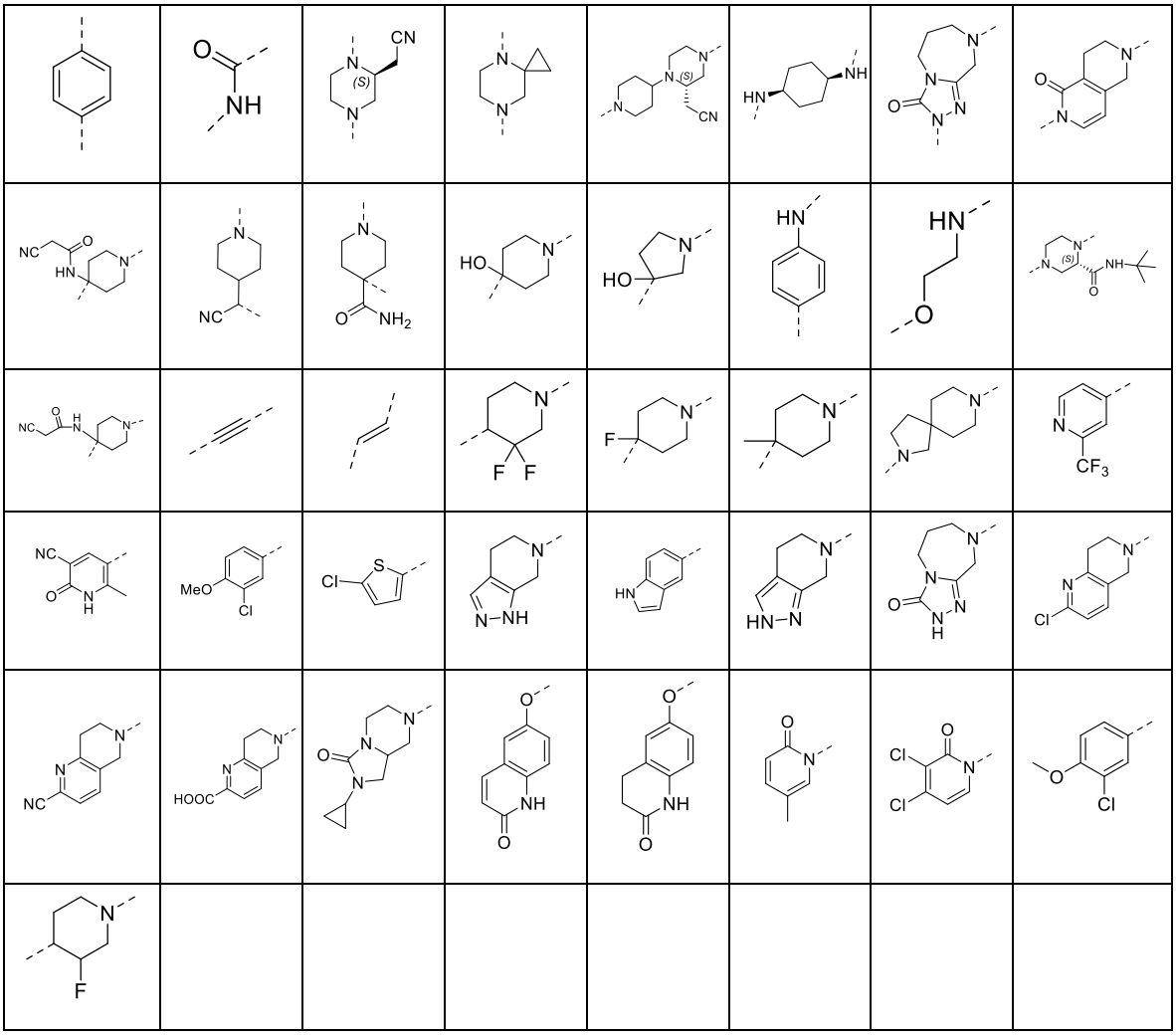
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

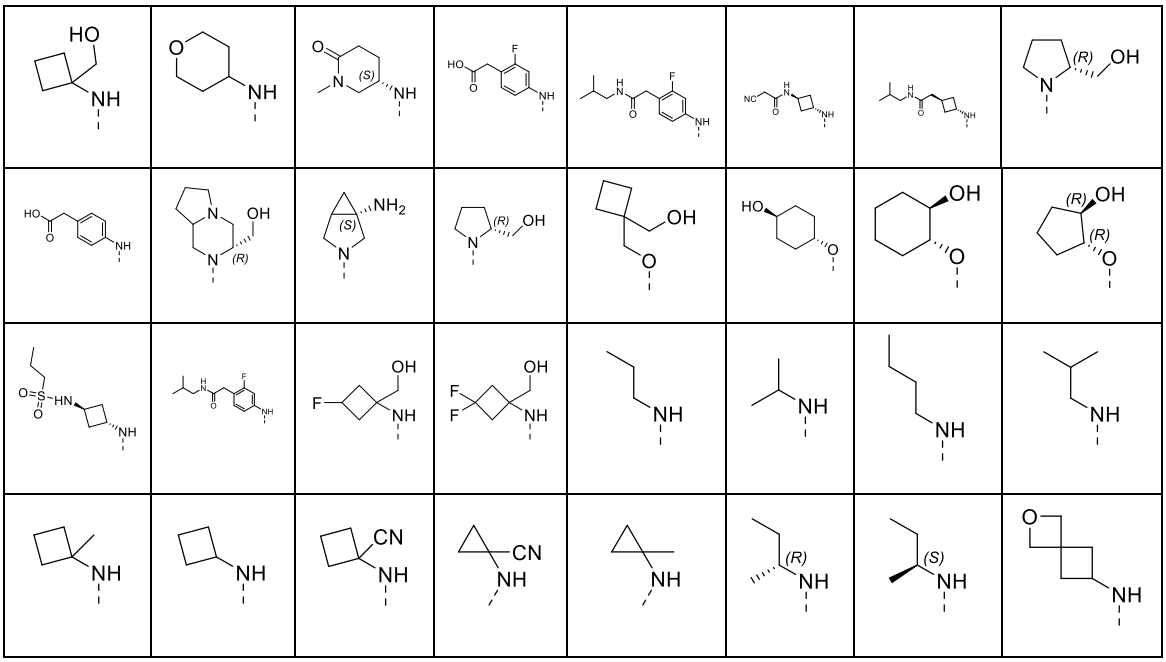
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

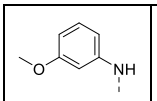
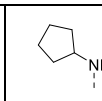
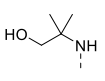
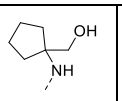
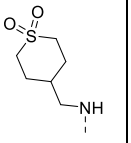
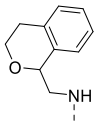
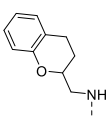
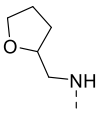
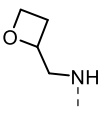
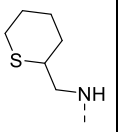
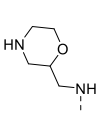
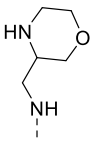
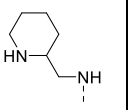
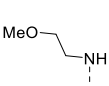
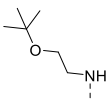
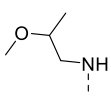
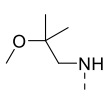
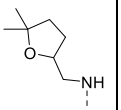
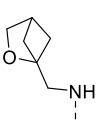
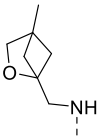
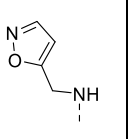
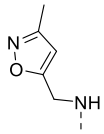
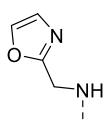
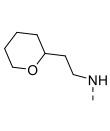
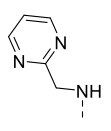
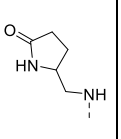
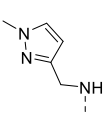
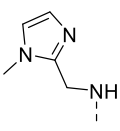
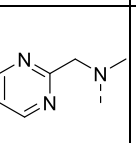
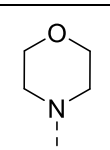
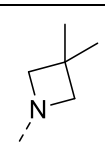
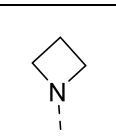
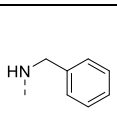
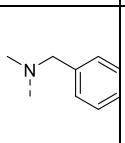
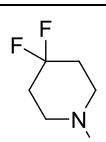
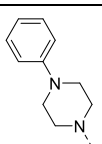
for example, ring A may be selected from the following groups:

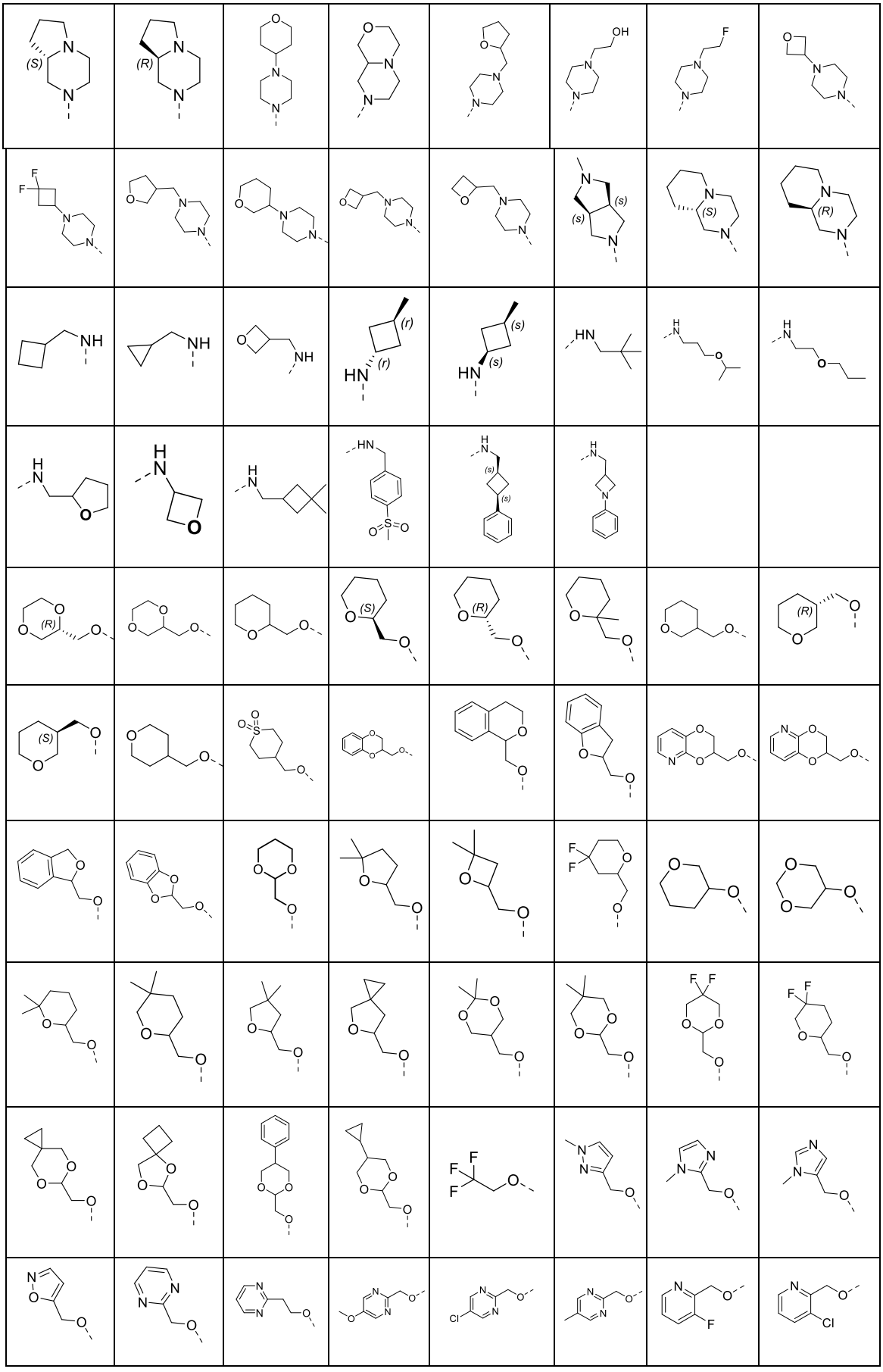


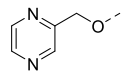
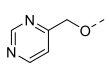
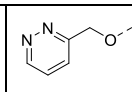
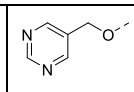
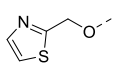
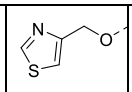
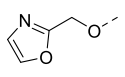
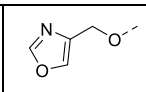
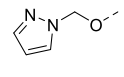
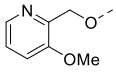
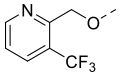
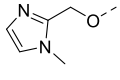
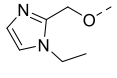
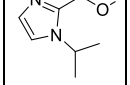
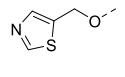
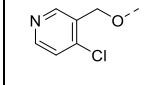
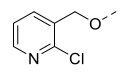
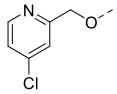
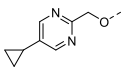
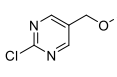
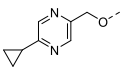
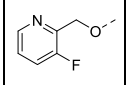
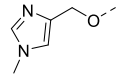
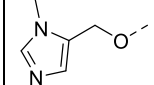
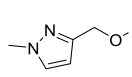
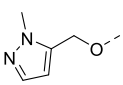
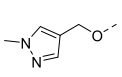
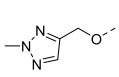
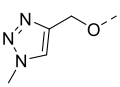
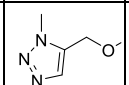
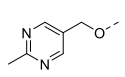
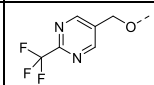
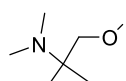
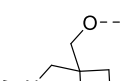
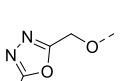
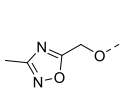
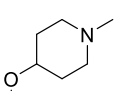
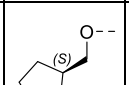
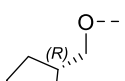
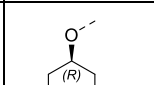


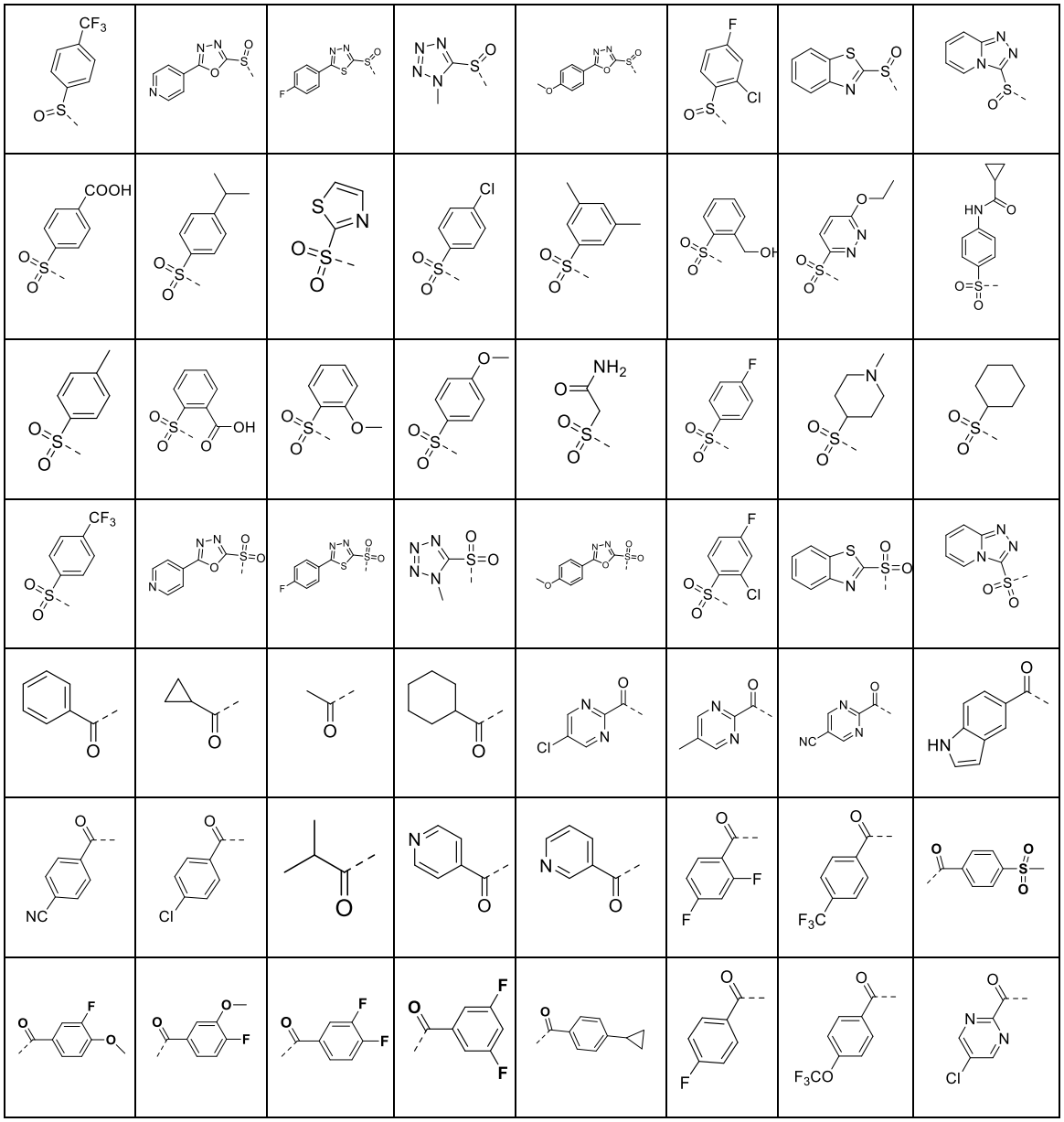
for example, -W-$R_2R_{2'}$ may be selected from the following groups:







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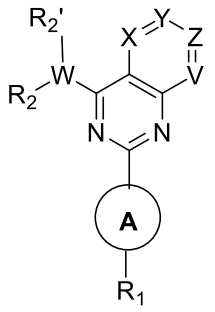
7. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula V has the following definitions:



V

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

V represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

or,

R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, $SO\text{-}R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring,

5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

wherein $R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2$CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$; or,

R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two,

or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, $SR^{2.1}$, $C_{1\text{-}3}$ alkyl-$SR^{2.1}$, SO-$R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

wherein $R^{2.1}$ is H or a group selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl alcohol, $C_{1\text{-}3}$ haloalkyl, a mono- or bicyclic ring, -$C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-($C_{1\text{-}3}$ alkyl), halogen, $C_{1\text{-}10}$ alkyl, and $C_{6\text{-}20}$ aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from $C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, $CO\text{-}NH_2$, $CO\text{-}NH\text{-}CH_3$, -$CO\text{-}N(CH_3)_2$, SO_2-($C_{1\text{-}3}$ alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $COOR^{2.1}$; or

$R_{2'}$ represents H, F, Me, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $C_{6\text{-}10}$ aryl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, $C_{5\text{-}10}$ heteroaryl-$C_{1\text{-}6}$ alkyl, a $C_{3\text{-}10}$ heterocyclic ring, a $C_{5\text{-}10}$ heterocyclic ring, -NR'R'', fluorine, $C_{1\text{-}6}$ fluoroalkyl, and $C_{1\text{-}6}$ fluoroalkoxy, wherein R' and R'' are independently selected from H and $C_{1\text{-}6}$ alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, $C_{1\text{-}6}$ alkyl, and O-$C_{1\text{-}6}$ alkyl;

or,

R_2 and $R_{2'}$ together form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially

saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, $SO\text{-}R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

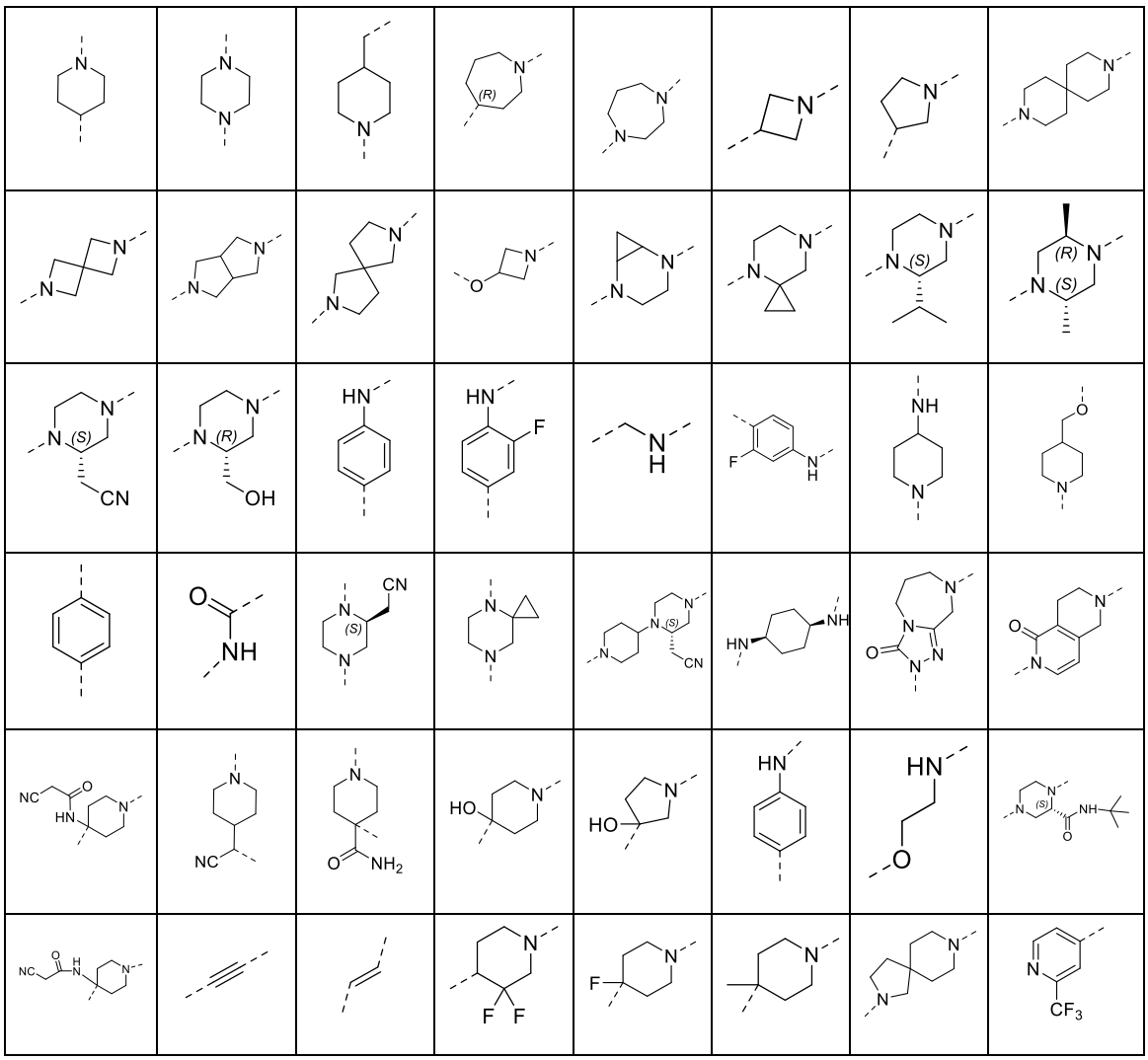
the cycloalkyl may be saturated or partially saturated;

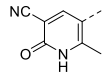
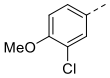
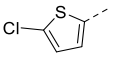
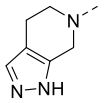
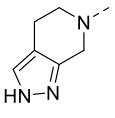
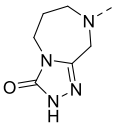
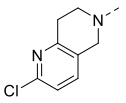
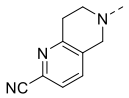
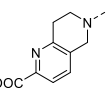
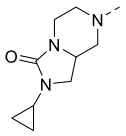
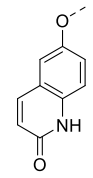
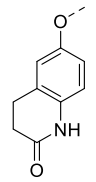
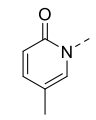
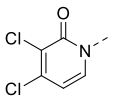
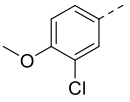
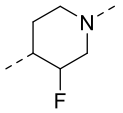
$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl,

3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

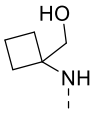
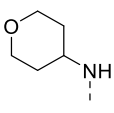
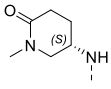
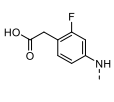
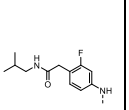
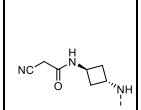
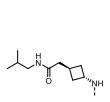
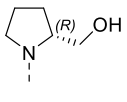
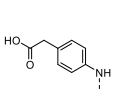
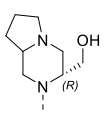
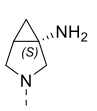
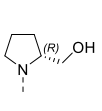
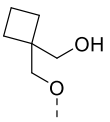
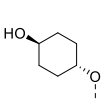
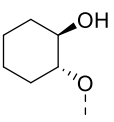
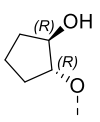
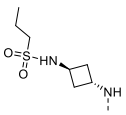
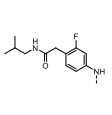
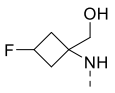
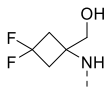
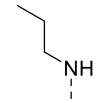
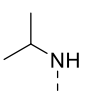
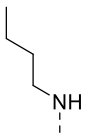
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

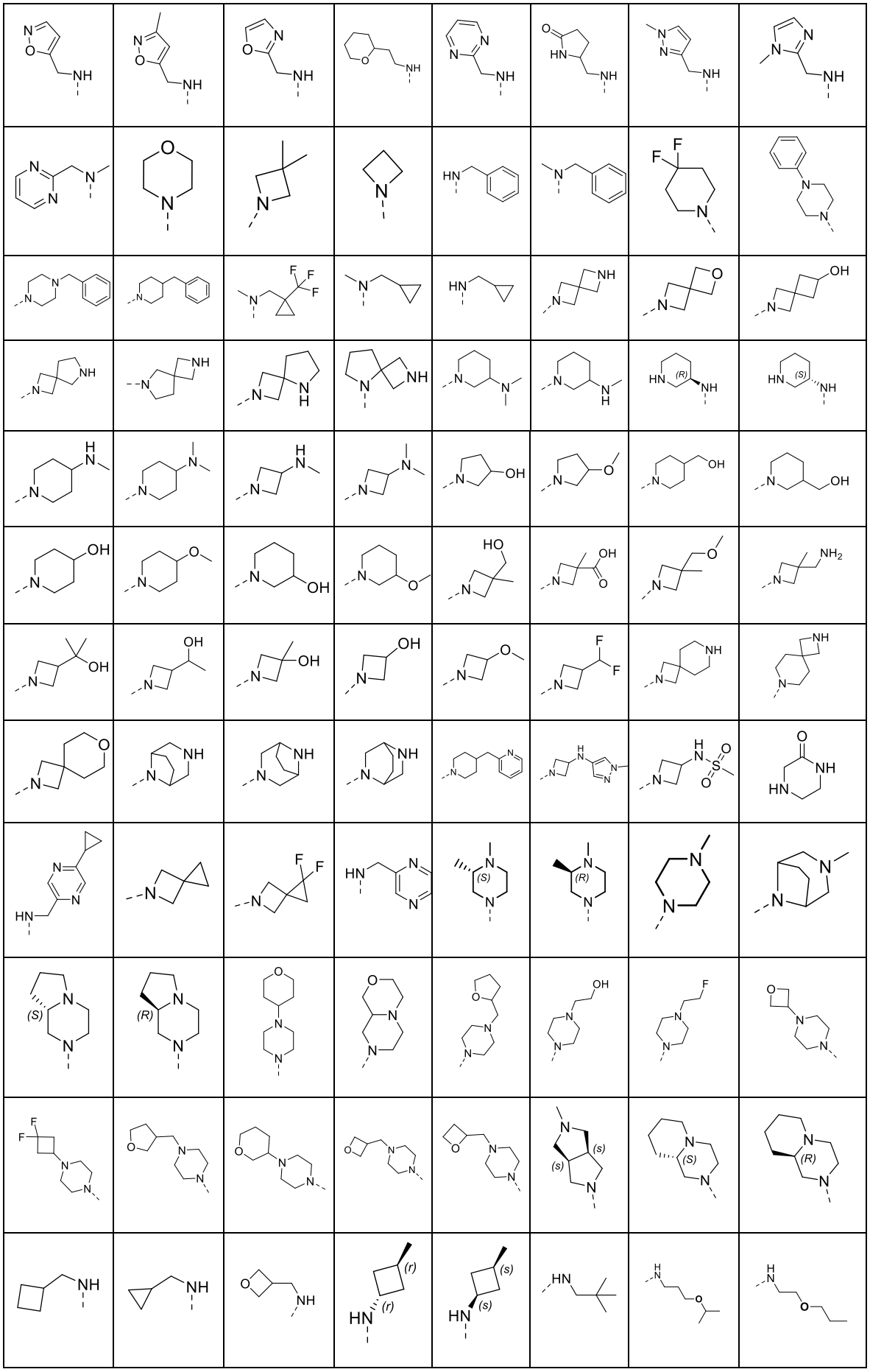
for example, ring A may be selected from the following groups:

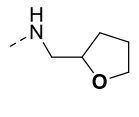
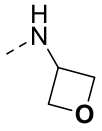
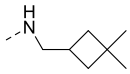
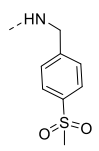
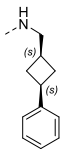
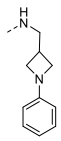
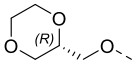
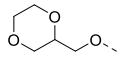
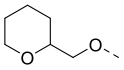
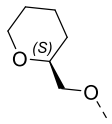
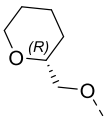
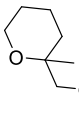
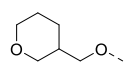
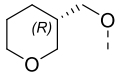
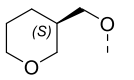
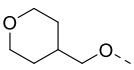
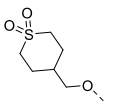
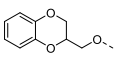
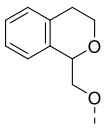
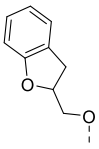
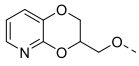
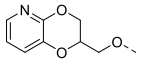
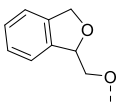
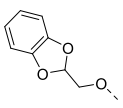
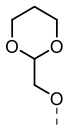
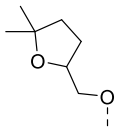
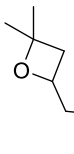
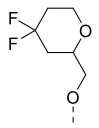
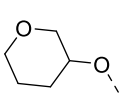
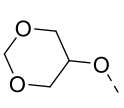
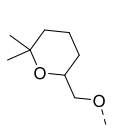
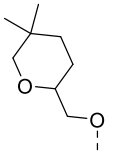
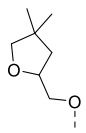
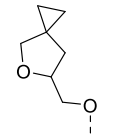
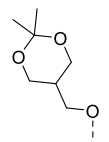
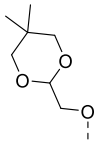
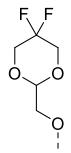
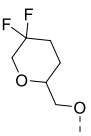
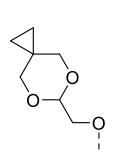
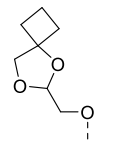


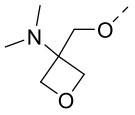
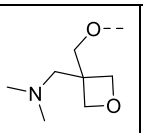
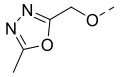
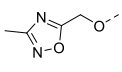
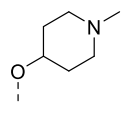
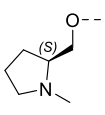
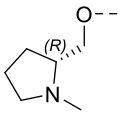
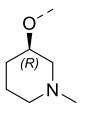
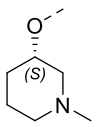
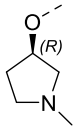
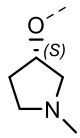
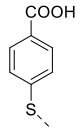
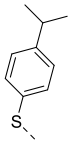
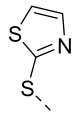
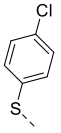
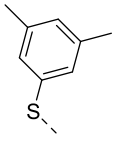
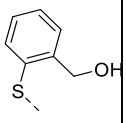
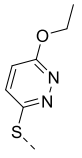
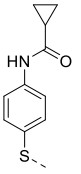
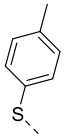
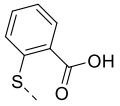
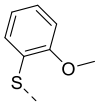
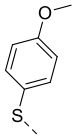
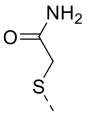
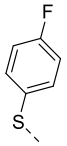
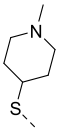
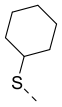
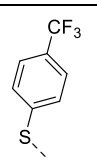
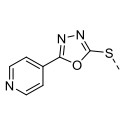
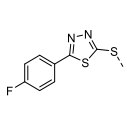
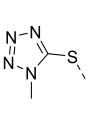
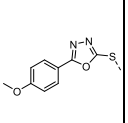
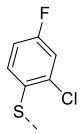
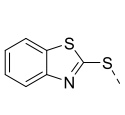
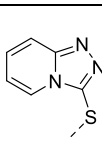
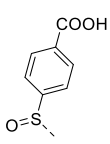
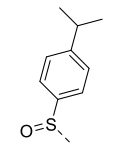
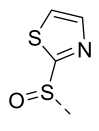
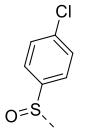
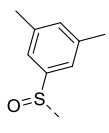
							
							
							

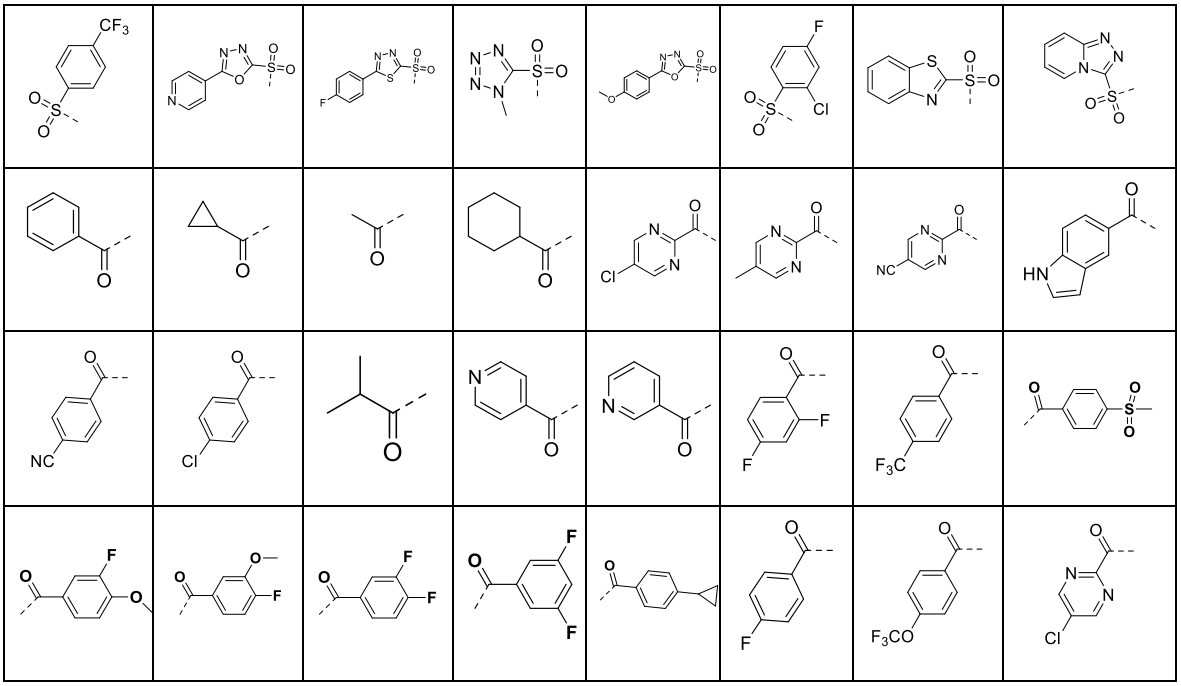
for example, the substituent -W-R_2R_2, may be selected from the following groups:





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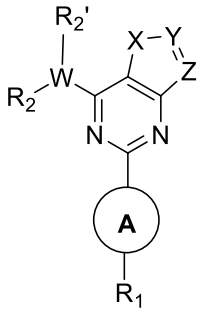
8. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula VI has the following definitions:



VI

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), $C_{1\text{-}2}$ alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic $C_{6\text{-}20}$ aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$,

CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

or,

R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2,

CO-NH-CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$; or

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $NR^{2.2}R^{2.3}$, $CH_2\text{-}NR^{2.2}R^{2.3}$, $CH_2CH_2\text{-}NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and $SO_2\text{-}NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH{=}CHCO\text{-}NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl,

3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$;

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered

heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

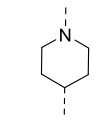
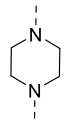
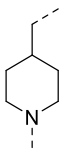
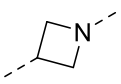
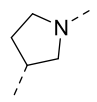
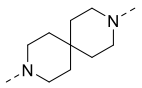
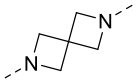
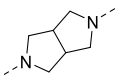
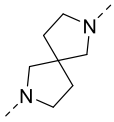
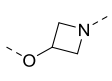
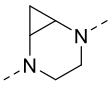
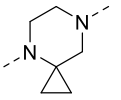
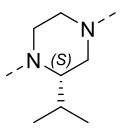
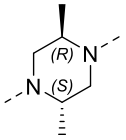
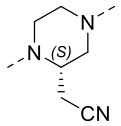
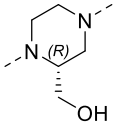
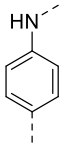
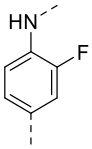
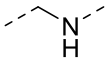
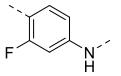
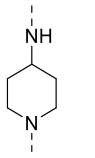
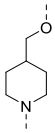
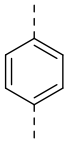
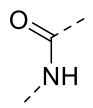
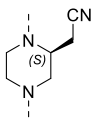
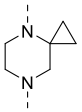
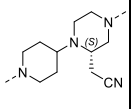
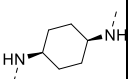
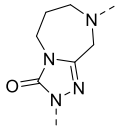
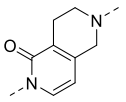
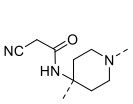
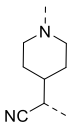
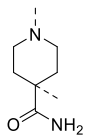
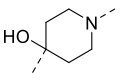
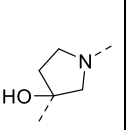
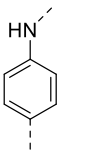
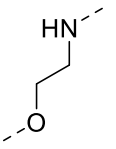
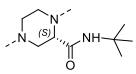
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

for example, ring A may be selected from the following groups:

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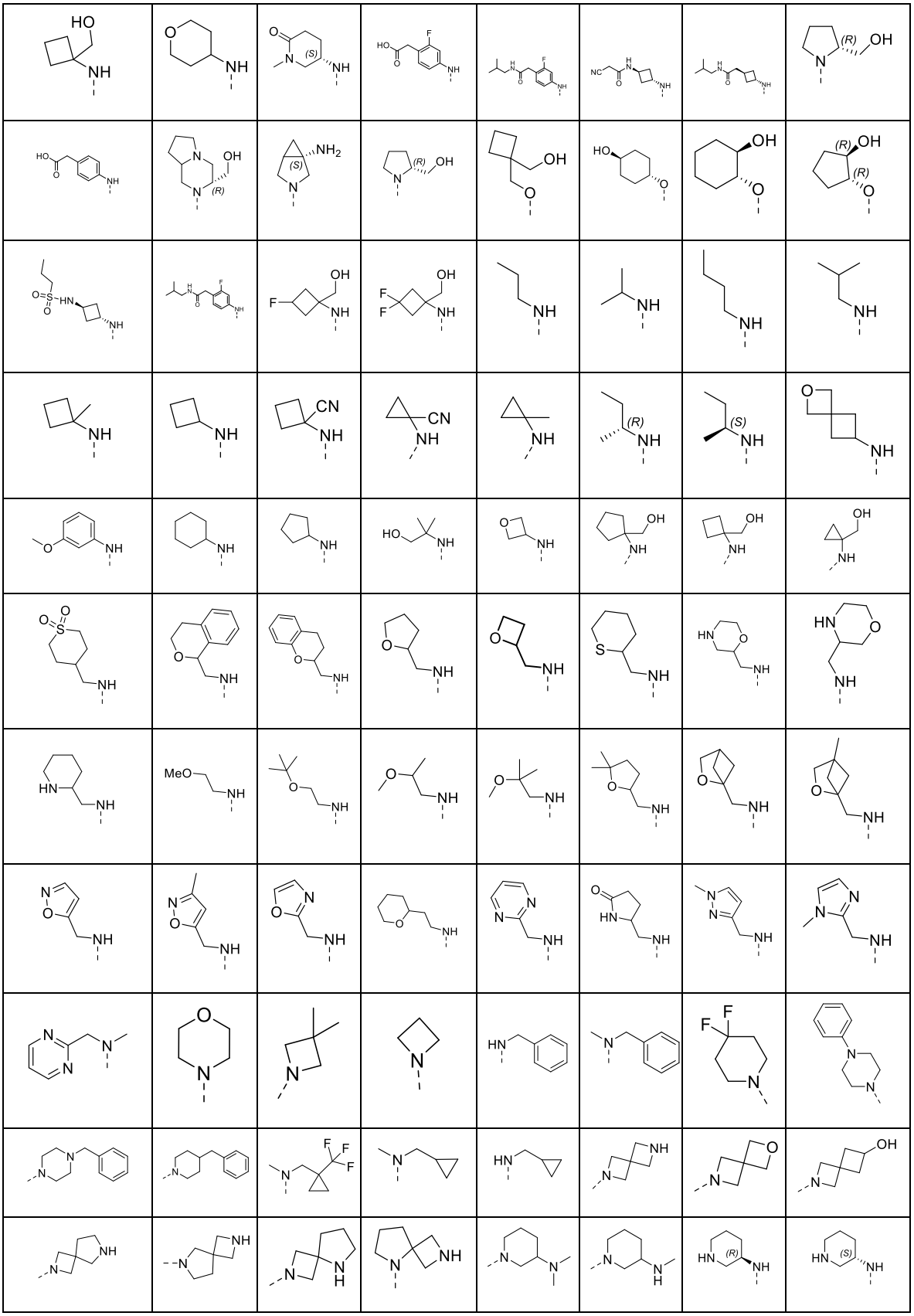

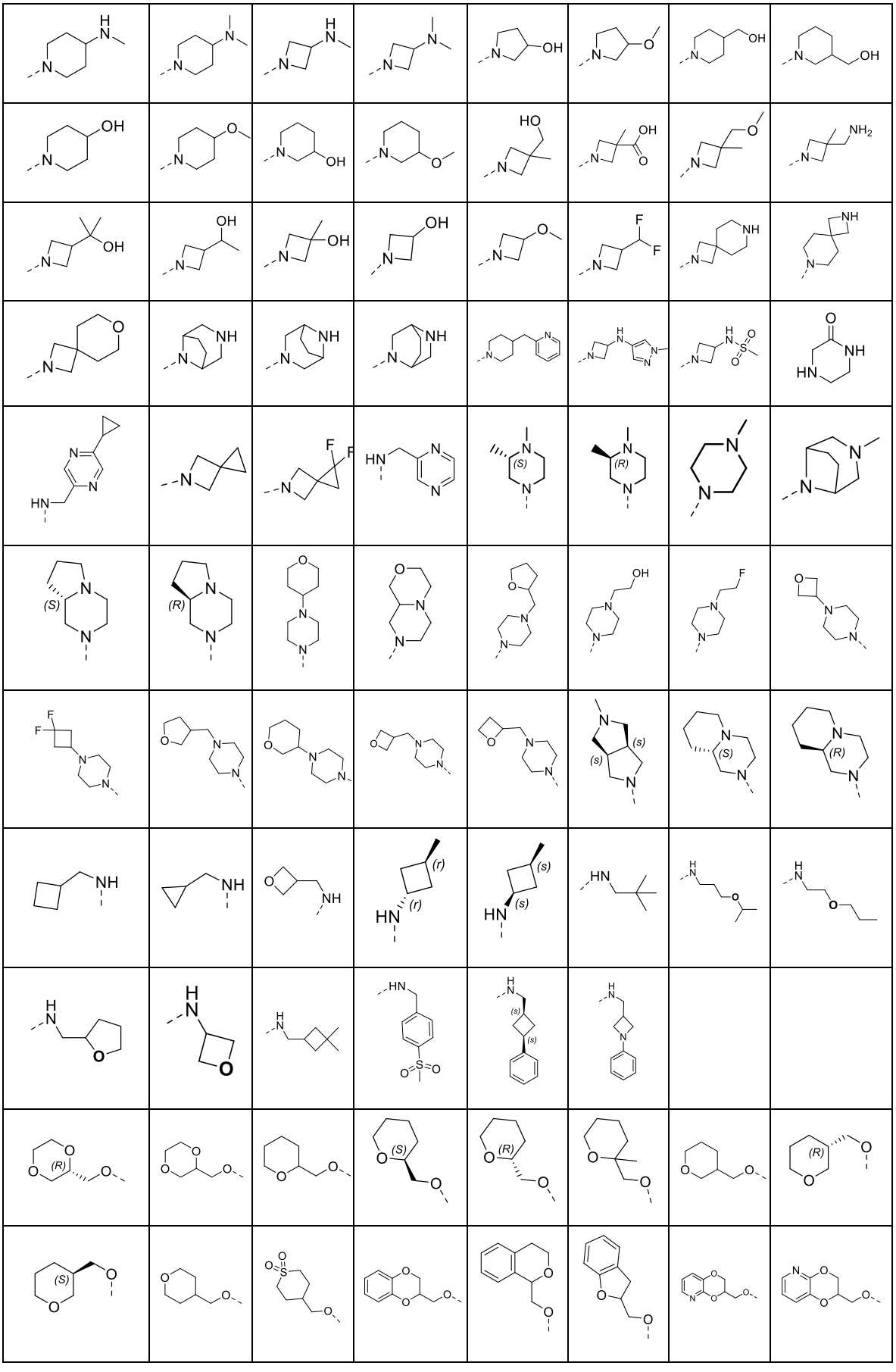

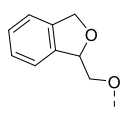	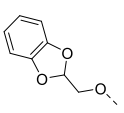	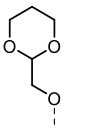	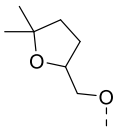	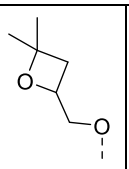	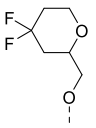	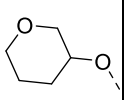	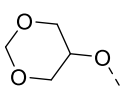
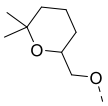	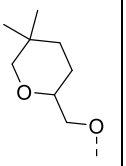	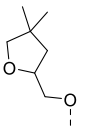	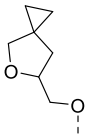	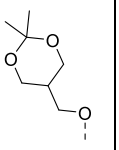	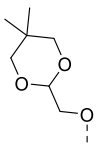	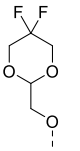	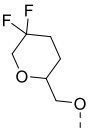
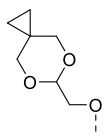	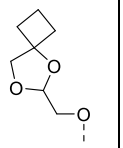	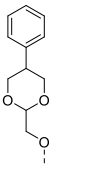	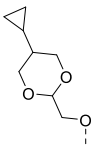	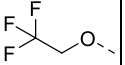	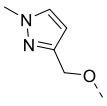	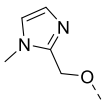	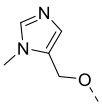
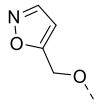	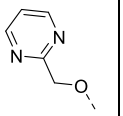	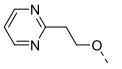	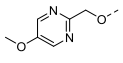	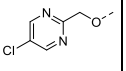	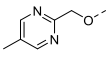	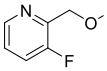	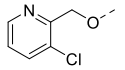
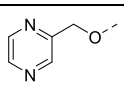	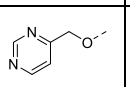	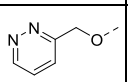	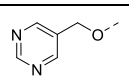	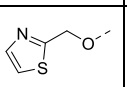	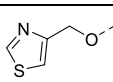	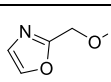	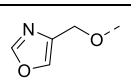

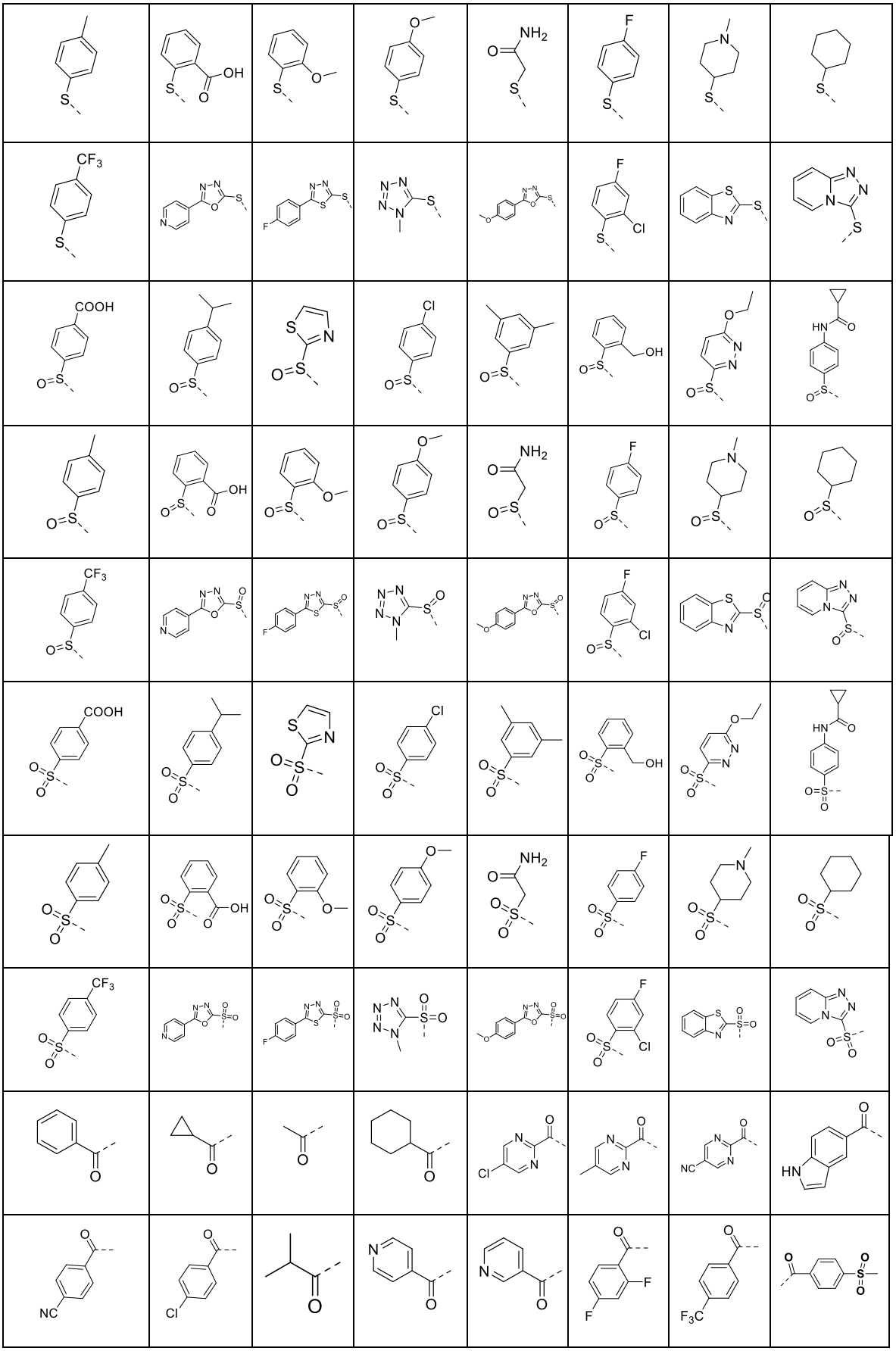

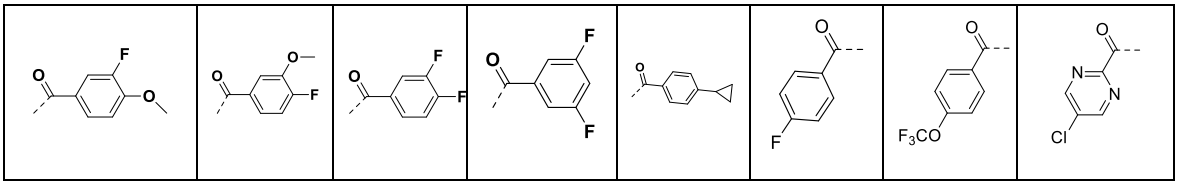

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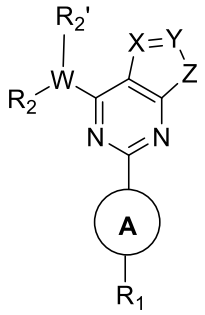
9. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula VII has the following definitions:



VII

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), $C_{1\text{-}2}$ alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic $C_{6\text{-}20}$ aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, $C_{3\text{-}10}$ cycloalkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ fluoroalkyl, CF_3, CHF_2, CH_2F, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two,

or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $C_{1\text{-}3}$ alkyl-$OR^{1.1}$, $SR^{1.1}$, $C_{1\text{-}3}$ alkyl-$SR^{1.1}$, SO-$R^{1.1}$, $C_{1\text{-}3}$ alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, $C_{1\text{-}3}$ alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl alcohol, $C_{1\text{-}3}$ haloalkyl, a mono- or bicyclic ring, -$C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-($C_{1\text{-}3}$ alkyl), halogen, $C_{1\text{-}10}$ alkyl, and $C_{6\text{-}20}$ aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from $C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, $CO\text{-}NH_2$, CO-NH.CH_3, -$CO\text{-}N(CH_3)_2$, SO_2-($C_{1\text{-}3}$ alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $COOR^{1.1}$;

R_2 represents hydrogen or a mono- or polycyclic $C_{6\text{-}20}$ aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, $C_{3\text{-}10}$ cycloalkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, $C_{1\text{-}$

$_6$ alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents is optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$; or

$R_{2'}$ represents H, F, Me, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl,

C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=$CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=$CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=$CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl

alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

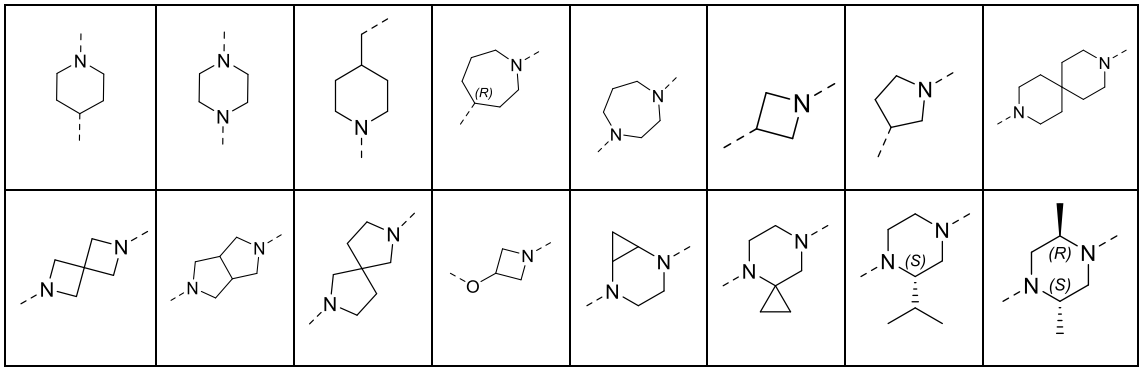
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

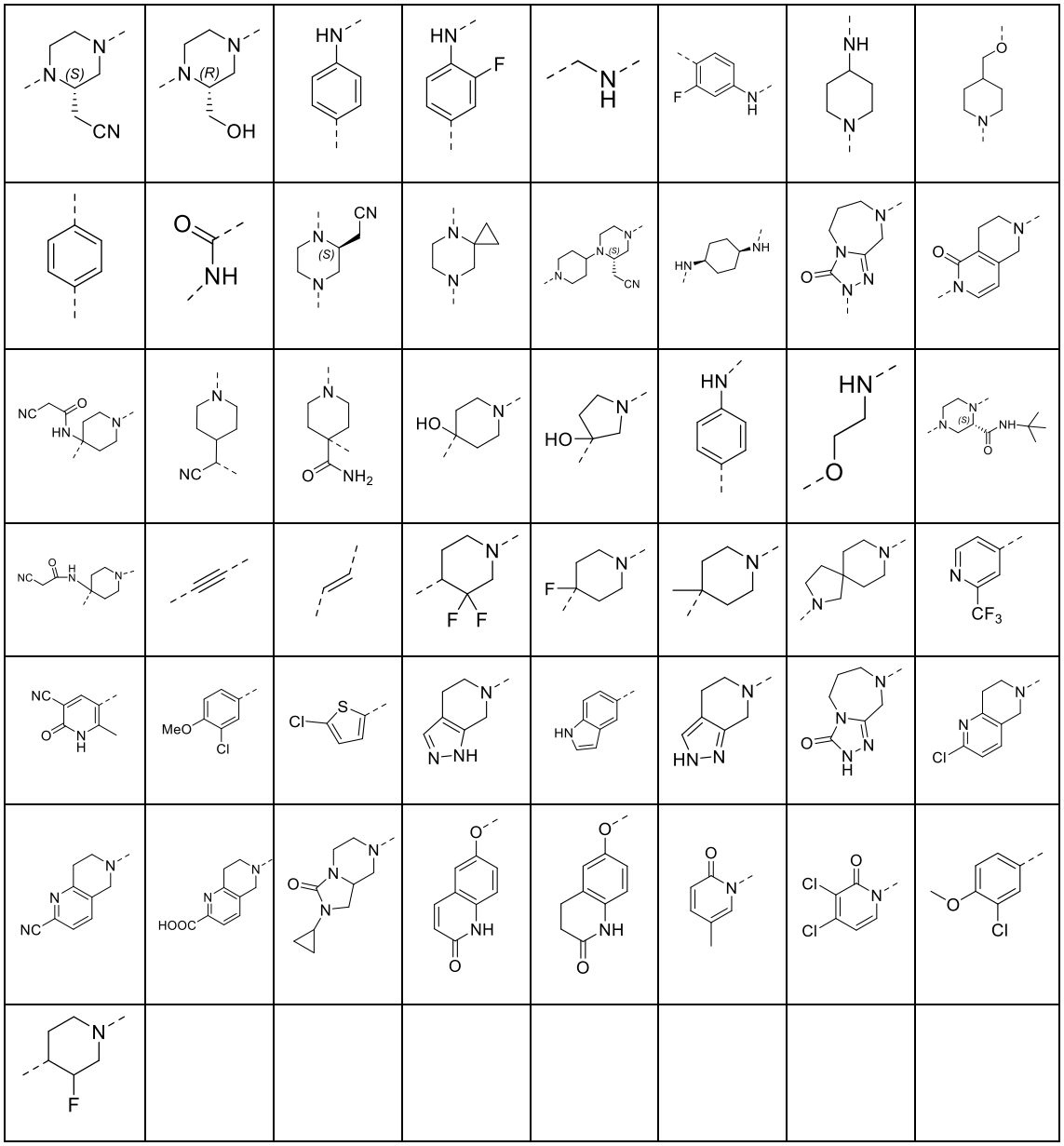
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

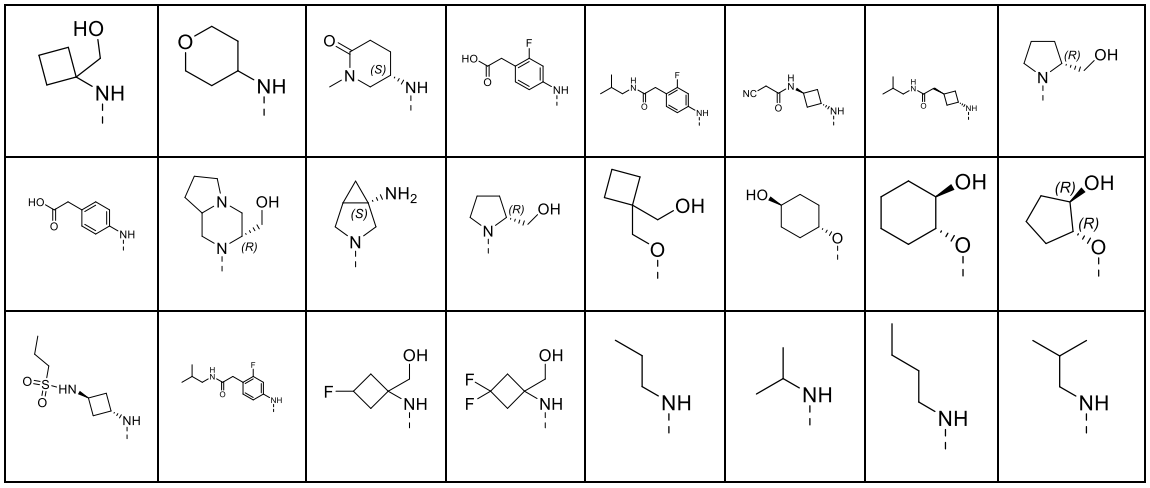
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

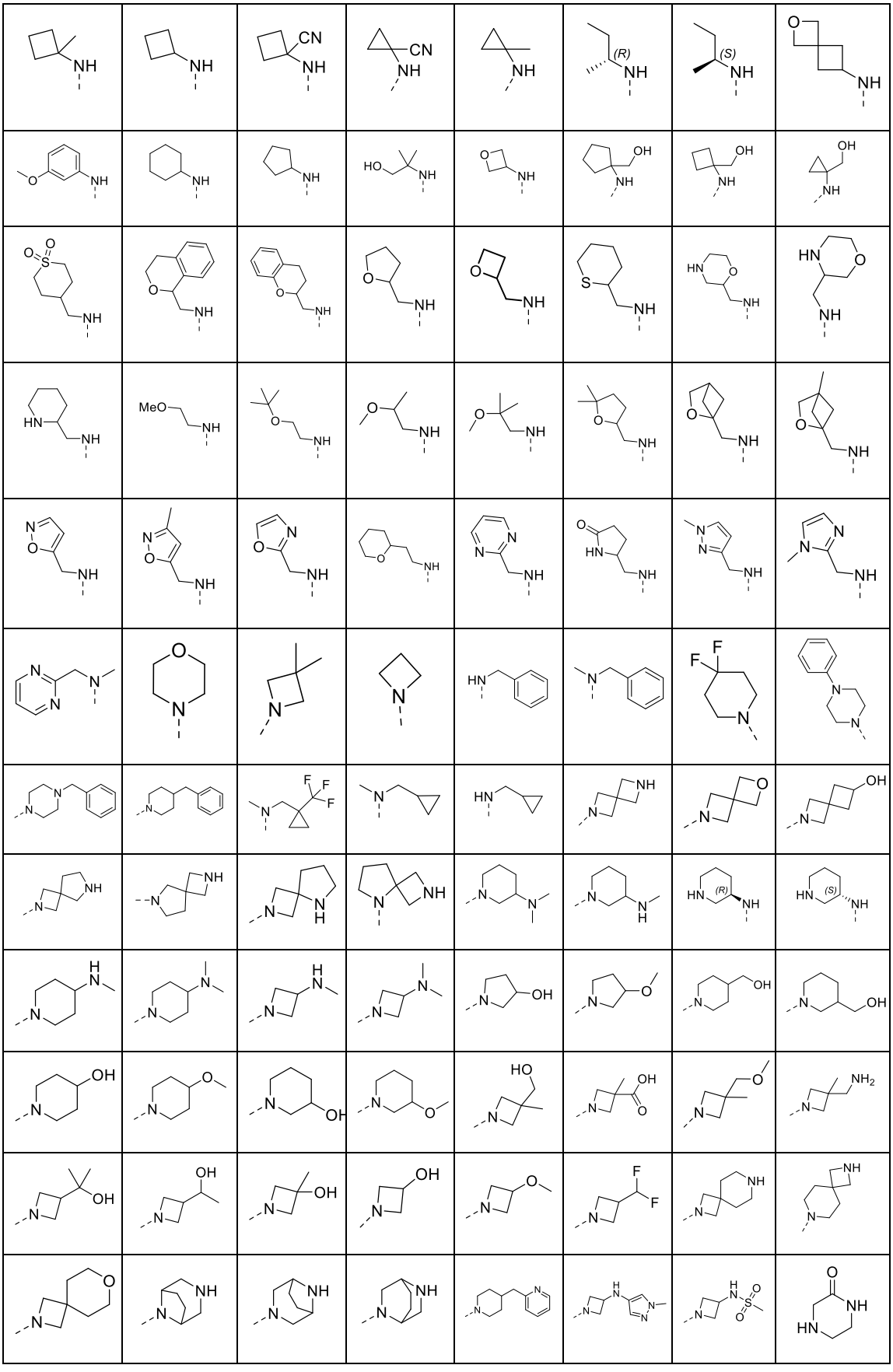
for example, ring A may be selected from the following groups:

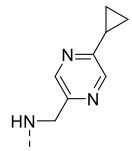
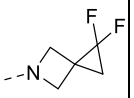
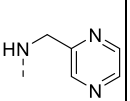
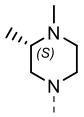
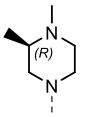
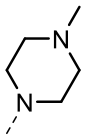
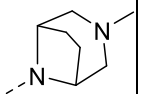
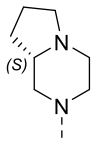
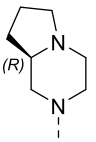
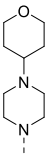
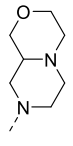
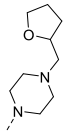
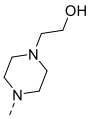
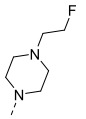
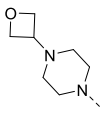
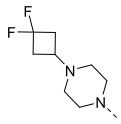
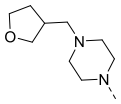
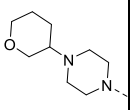
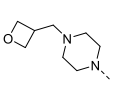
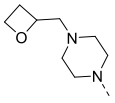
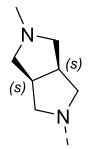
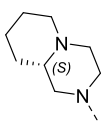
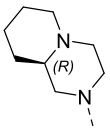
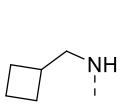
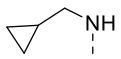
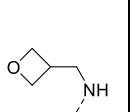
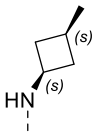
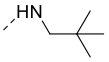
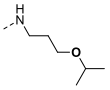
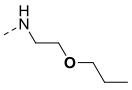
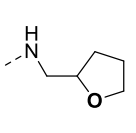
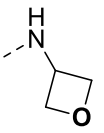
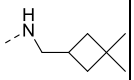
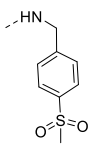
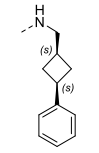
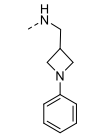
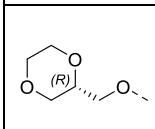
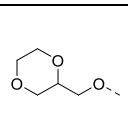


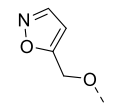
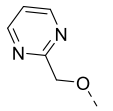
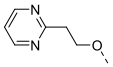
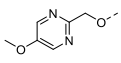
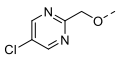
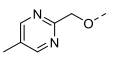
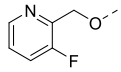
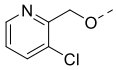
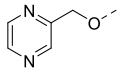
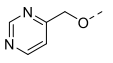
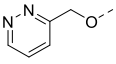
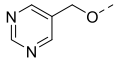
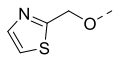
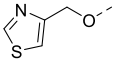
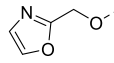
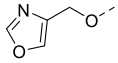
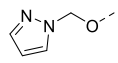
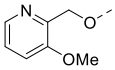
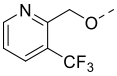
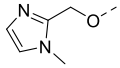
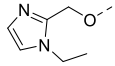
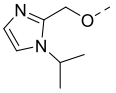
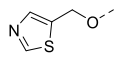
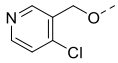
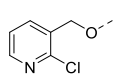
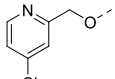
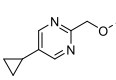
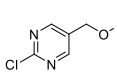
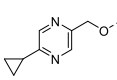
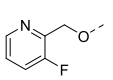
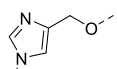
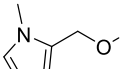
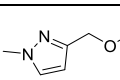
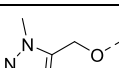
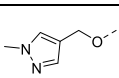
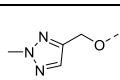
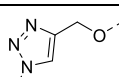
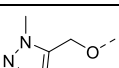
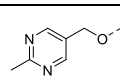
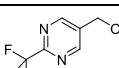


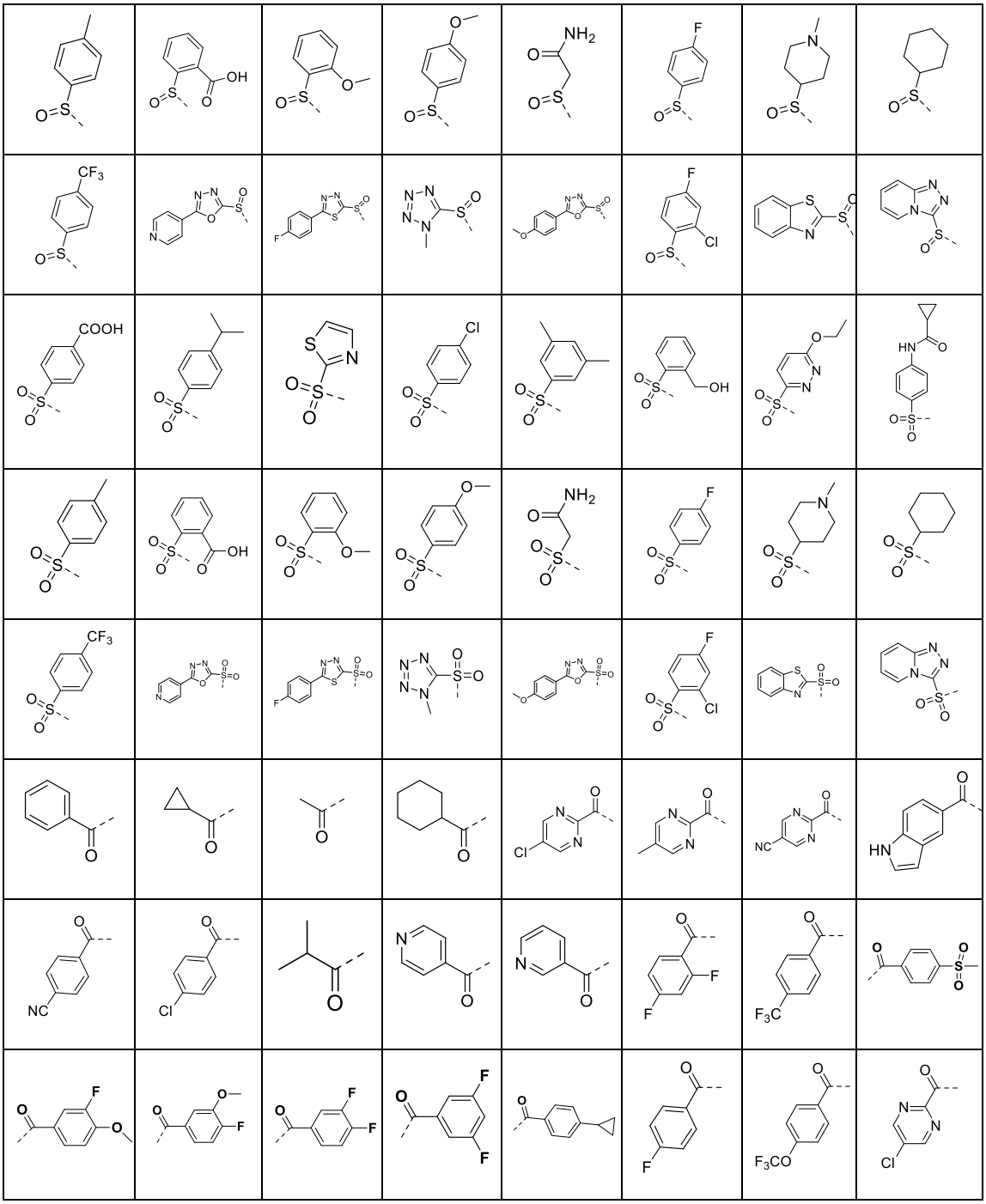
for example, the group -W-R_2R_2, may be selected from the following groups:







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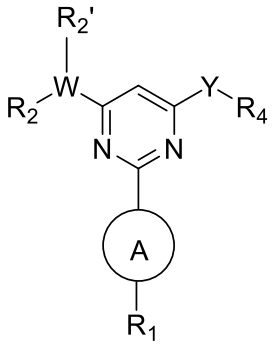
10. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula VIII has the following definitions:



VIII

W represents CH, O, S, N, S(O), $S(O)_2$, C(O), C_{1-2} alkyl, ethenyl, or ethynyl;

X represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Y represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

Z represents CH_2, O, S, NH, S(O), $S(O)_2$, or C(O);

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

or R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, $SO\text{-}R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, $SO_2\text{-}R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH{=}CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3,

CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10} cycloalkyl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{2.2}R^{2.3}$;

or R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$,

$CH=CHCOOR^{2.1}$, $CO\text{-}NR^{2.1}CH_2CO\text{-}NR^{2.1}$, $CH_2CH_2CO\text{-}NR^{2.1}$, $CH=CHCO\text{-}NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, $C_{1\text{-}6}$ alkyl alcohol, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, $C_{1\text{-}3}$ alkyl-(monocyclic or polycyclic $C_{6\text{-}20}$ aryl), 3- to 20-membered heterocyclyl-$C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl $C_{1\text{-}3}$ alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}10}$ aryl, and $NR^{2.2}R^{2.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the cycloalkyl may be saturated or partially saturated;

$R^{2.1}$ is H or a group selected from $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkyl alcohol, $C_{1\text{-}3}$ haloalkyl, a mono- or bicyclic ring, -$C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, 3- to 20-membered heterocyclic-$C_{1\text{-}6}$ alkyl, $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-($C_{1\text{-}3}$ alkyl), halogen, $C_{1\text{-}10}$ alkyl, and $C_{6\text{-}20}$ aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from $C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{3\text{-}10}$ cycloalkyl, $C_{6\text{-}20}$ aryl-$C_{1\text{-}6}$ alkyl, 5- to 20-membered heteroaryl-$C_{1\text{-}6}$ alkyl, mono- or bicyclic $C_{6\text{-}20}$ aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, $CO\text{-}NH_2$, $CO\text{-}NH\text{-}CH_3$, $\text{-}CO\text{-}N(CH_3)_2$, SO_2-($C_{1\text{-}3}$ alkyl), $CO\text{-}R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, $C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ aryl, and $COOR^{2.1}$;

$R_{2'}$ represents H, F, Me, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $C_{6\text{-}10}$ aryl, $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkyl, $C_{6\text{-}20}$ heteroaryl-$C_{1\text{-}6}$ alkyl, a $C_{3\text{-}10}$ heterocyclic ring, a $C_{6\text{-}20}$ heterocyclic ring, -NR'R'', fluorine, $C_{1\text{-}6}$ fluoroalkyl, and $C_{1\text{-}6}$ fluoroalkoxy, wherein R' and R'' are independently selected from H and $C_{1\text{-}6}$ alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, $C_{1\text{-}6}$ alkyl, and O-$C_{1\text{-}6}$ alkyl;

or R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F,

$OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$;

R_4 represents a group selected from aryl and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or independently and optionally substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$;

ring A represents a chemical bond or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-10} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

ring A represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents

selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH{=}CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2CO$-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, $CH{=}CHCO$-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

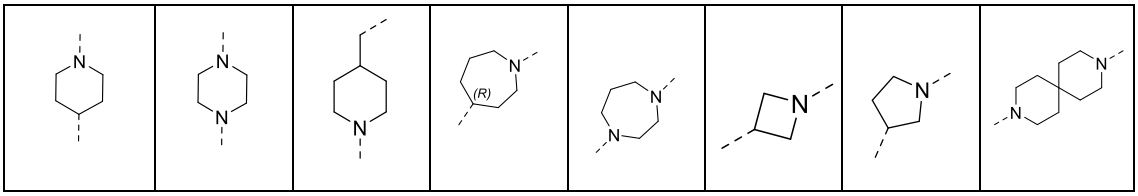
the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

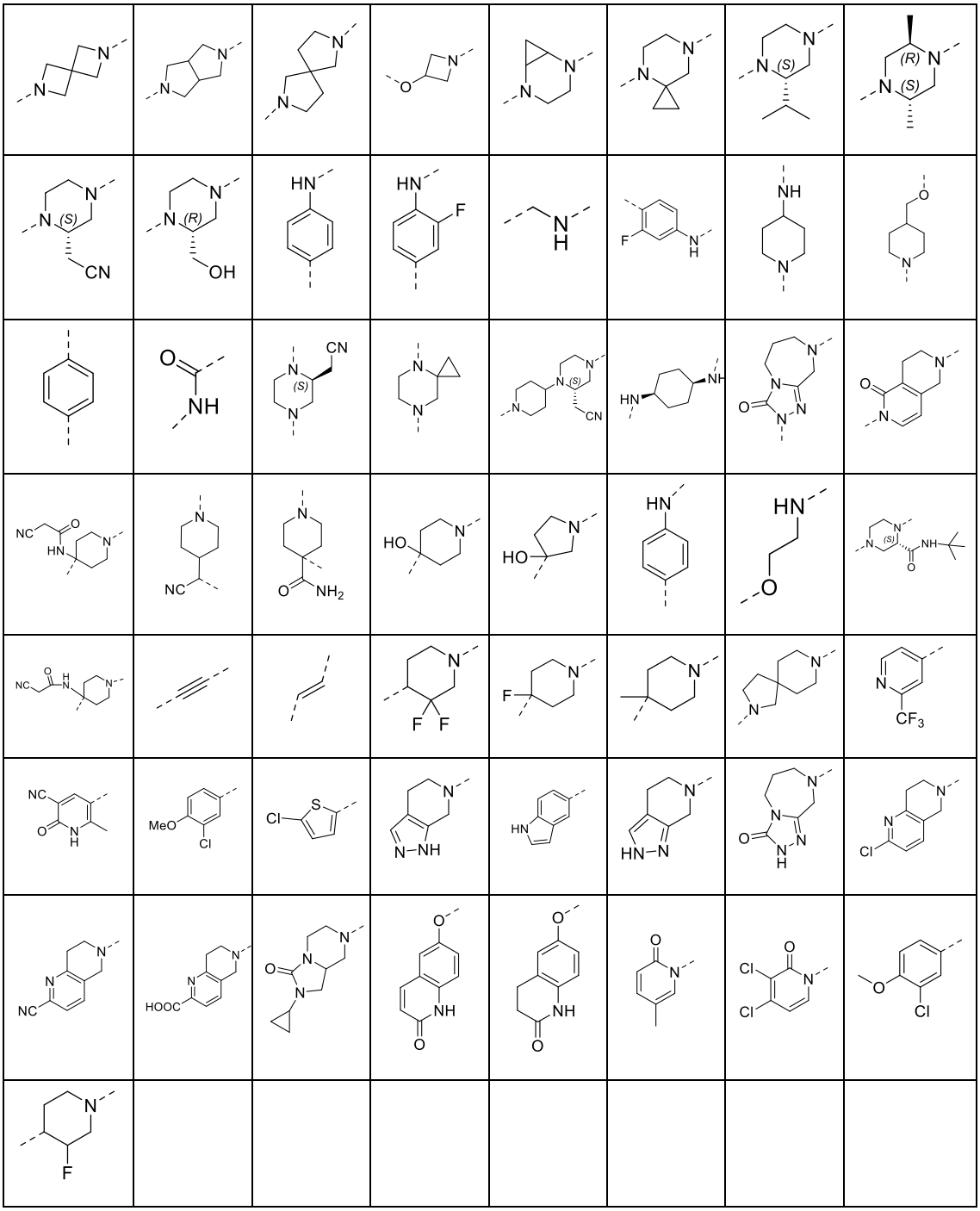
the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

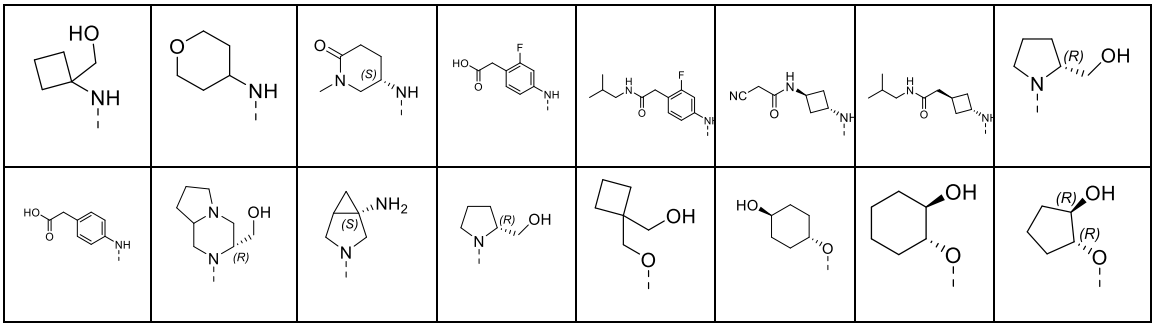
$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

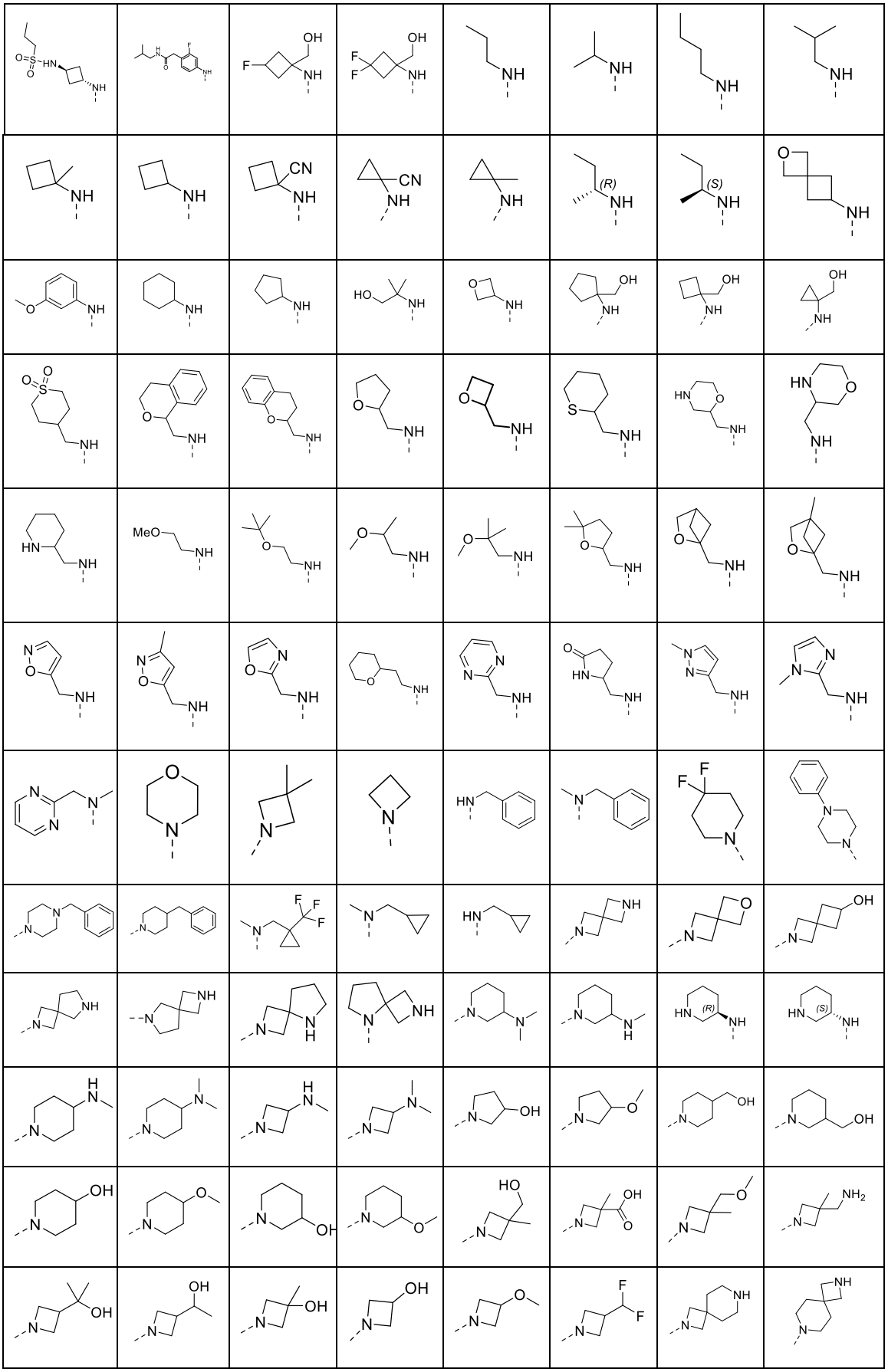
for example, ring A may be selected from the following groups:

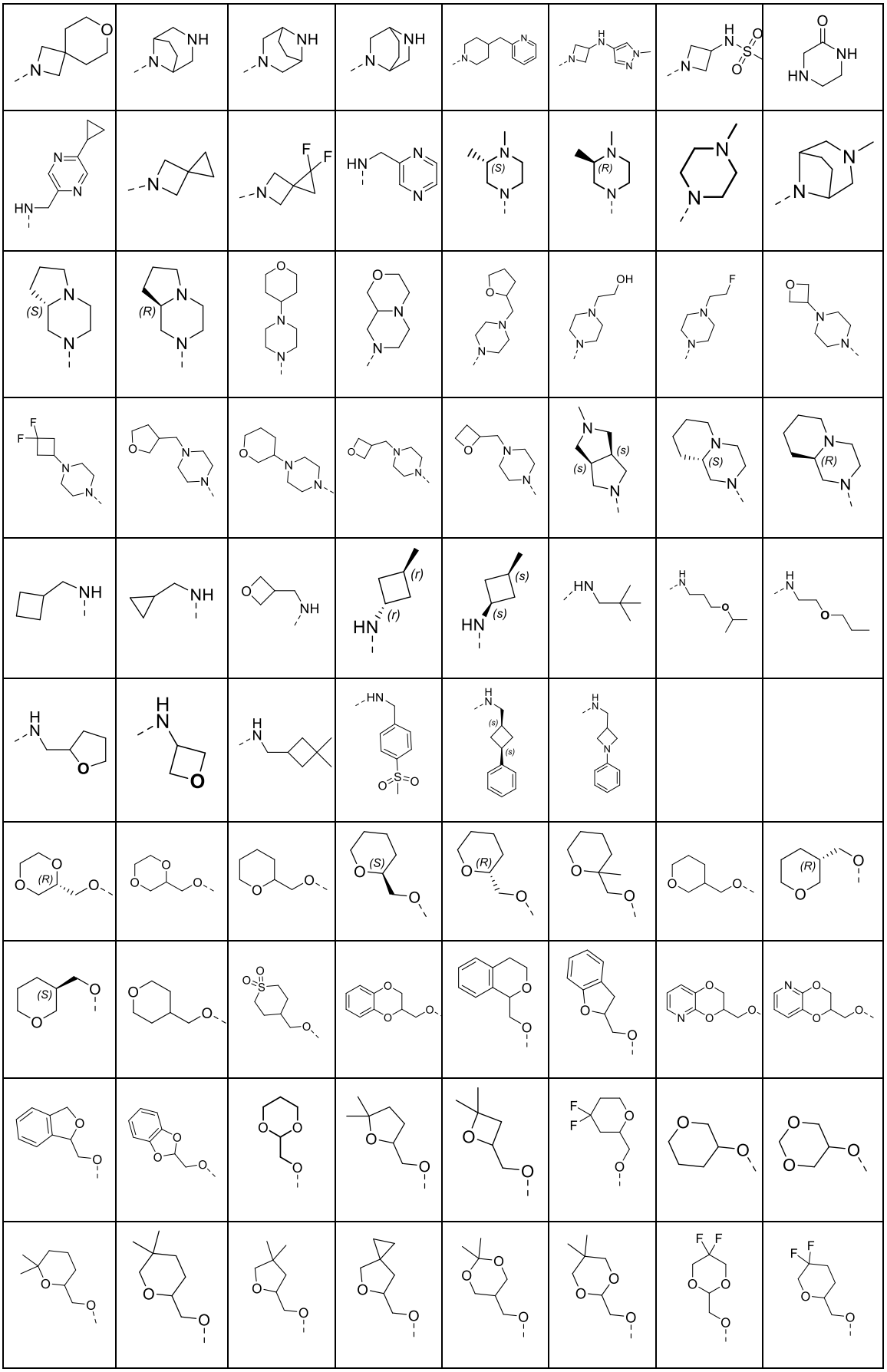


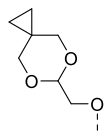
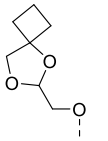
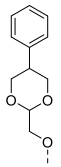
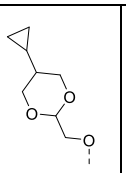
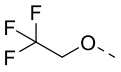
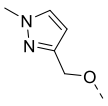
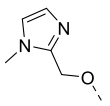
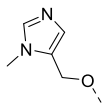
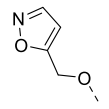
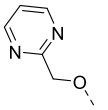
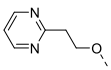
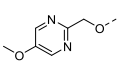
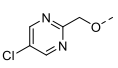
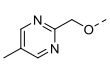
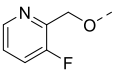
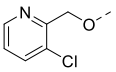
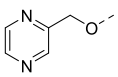
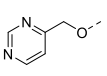
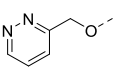
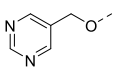
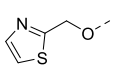
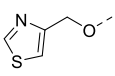
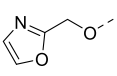
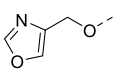
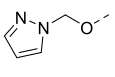
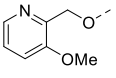
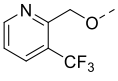
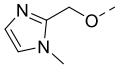
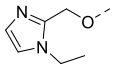
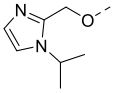
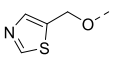
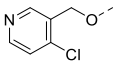
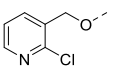
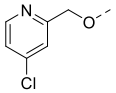
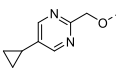
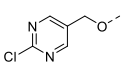
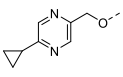
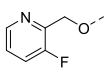
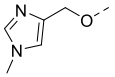
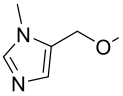


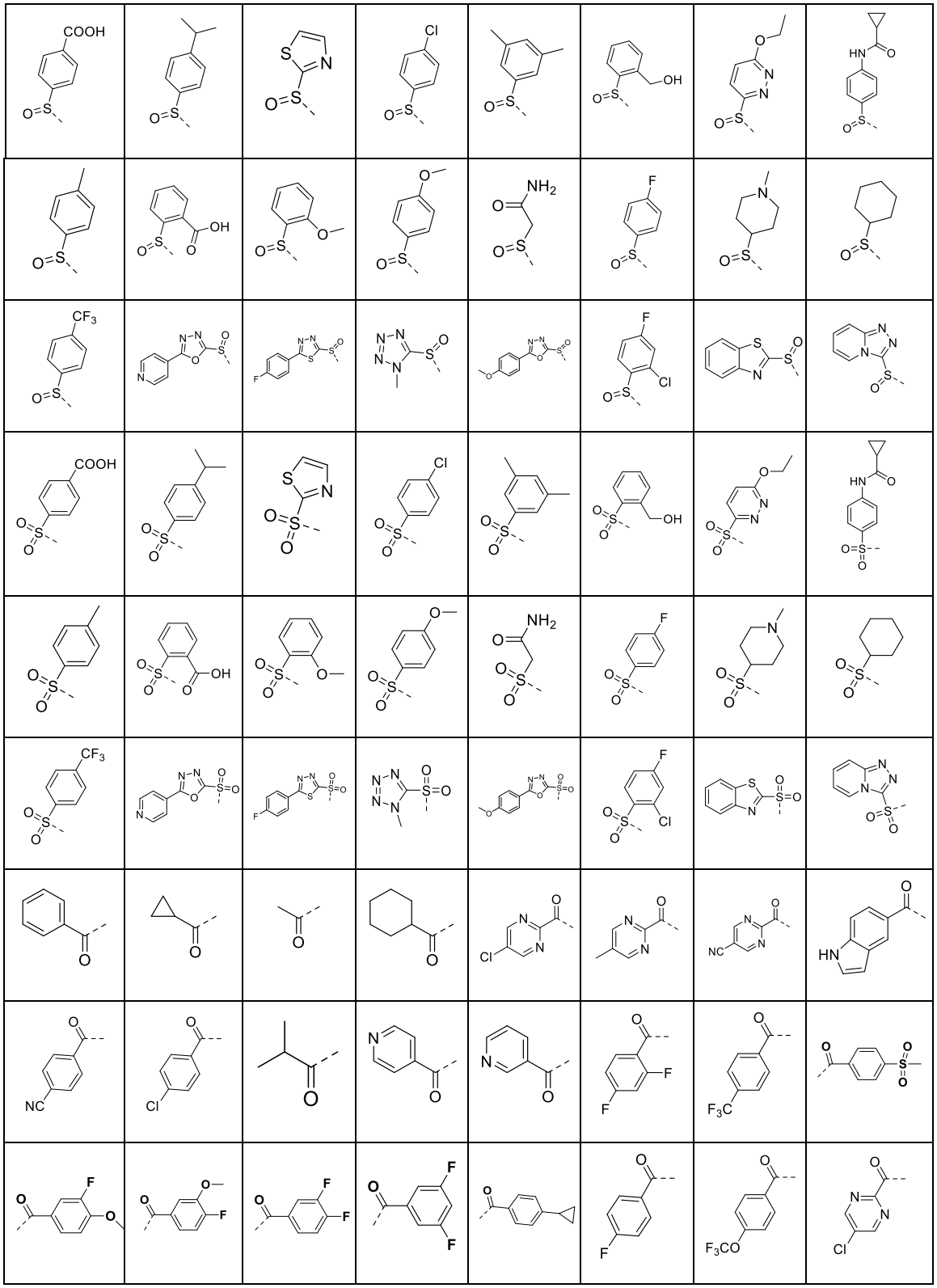
for example, the group -W-R_2R_2, may be selected from the following groups:









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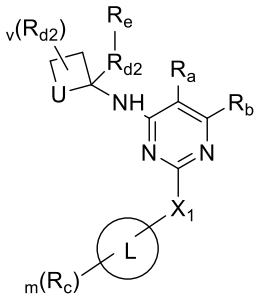
11. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to claim 2, wherein the compound of formula IX has the

following definitions:



IX

wherein:

X_1 represents a chemical bond, C_{1-20} alkylene, O, S, NR_q, S(=O), $S(=O)_2$, or C(=O);

U represents $-(CH_2)_t-$, O, S, NR_q, S(=O), $S(=O)_2$, or C(=O), wherein t represents 0, 1, 2, or 3;

R_q is selected from H, halogen, OH, CN, NO_2, NH_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, C_{1-8} heteroalkyl-fused C_{6-20} aryl-, C_{1-8} heteroalkyl-C_{6-20} aryl-, NH_2, $-C(O)R_{41}$, $-C(O)OR_{42}$, $-OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

v represents 0, 1, 2, 3, 4, or 5;

L represents a chemical bond, C_{2-20} alkynyl, or Cy, wherein L may be linked to X_1 or R_c at any position;

Cy represents a chemical bond, 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl, wherein the 3- to 20-membered heterocyclyl, C_{6-20} aryl, or 5- to 20-membered heteroaryl may be optionally fused to 4- to 7-membered cycloalkyl, provided that when the heterocyclyl contains an N atom, the heterocyclyl may be bonded to the carbon atom at the 2-position of the pyrimidine ring in formula IX via the N atom or a C atom thereof;

R_a represents H or $-X-R_3$;

X represents CH_2, O, S, NH, -S(O)-, $-S(O)_2-$, or -C(O)-;

R_3 represents H, halogen, OH, CN, $-CH_2CF_3$, $-NHR_{d4}$, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d4}: C_{1-20} alkyl, $-C(O)R_{61}$, $-C(O)OR_{62}$, $-OC(O)R_{63}$, and NH_2;

R_b represents H or $-Y-R_4$;

Y represents CH_2, O, S, NH, -S(O)-, -$S(O)_2$-, or -C(O)-;

R_4 represents H, halogen, OH, CN, -CH_2CF_3, -NHR_{d4}, or the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d5}: C_{1-20} alkyl, -$C(O)R_{61}$, -$C(O)OR_{62}$, -$OC(O)R_{63}$, and NH_2;

provided that R_a and R_b are not both H;

or R_a and R_b, together with the atoms linked thereto, form the following groups unsubstituted or optionally substituted with 1, 2, or more R_{d6}: C_{5-20} cycloalkenyl, 3- to 20-membered heterocyclyl, 5- to 20-membered heteroaryl, and 6- to 20-membered aryl;

R_{d2}, R_{d4}, R_{d5}, and R_{d6} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), SO, SO_2, and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, -$C(O)R_{31}$, -CH_2-$C(O)R_{31}$, -$C(O)OR_{32}$, -$CH_2C(O)OR_{32}$, -$C(O)NHR_{32}$, -$CH_2C(O)NHR_{32}$, -$OC(O)R_{33}$, -$S(O)_2R_{34}$, -$S(O)_2OR_{35}$, -$OS(O)_2R_{36}$, and -$P(O)(OR_{37})(OR_{38})$;

or when two or more substituents selected from R_{d2}, R_{d4}, R_{d5}, and R_{d6} are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_c are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl-O-C_{6-20} aryl-, 5- to 20-membered heteroaryl-N-C_{6-20} aryl-, 5- to 20-membered heteroaryl-S-C_{6-20} aryl-, 5- to 20-membered heteroaryl-CH_2-C_{6-20} aryl-, C_{4-10} cycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-fused C_{6-20} aryl-, C_{4-10} cycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl, C_{4-10} cycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-fused 5- to 20-membered

heteroaryl-, 4- to 10-membered heterocycloalkenyl-fused 5- to 20-membered heteroaryl-, C_{4-10} cycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-5- to 20-membered heteroaryl-, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{31}$, $-C(O)OR_{32}$, $-OC(O)R_{33}$, $-S(O)_2R_{34}$, $-S(O)_2OR_{35}$, $-OS(O)_2R_{36}$, and $-P(O)(OR_{37})(OR_{38})$;

for example, the 4- to 10-membered heterocycloalkyl or 4- to 10-membered heterocycloalkenyl may be: 1-methylpyrrolidinyl, 1-ethylpyrrolidinyl, 1-cyclopropylpyrrolidinyl, 1-cyclopropylmethylpyrrolidinyl, 5-methyl-4,5-dihydropyridazin-3(2H)-one, 1-methylazetidinyl, or 1-methylpiperidinyl;

m is selected from integers from 1 to 10;

R_e are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, NH_2, oxo (=O), thio (=S), $O\text{-}CONH_2$, $O\text{-}CONHR_f$, and the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, C_{1-8} heteroalkyl-fused C_{6-20} aryl-, C_{1-8} heteroalkyl-C_{6-20} aryl-, NH_2, $-C(O)R_{41}$, $-C(O)OR_{42}$, $-OC(O)R_{43}$, $-S(O)_2R_{44}$, $-S(O)_2OR_{45}$, $-OS(O)_2R_{46}$, and $-P(O)(OR_{47})(OR_{48})$;

or when two or more substituents selected from R_e are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_f: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_f are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl,

C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{51}$, $-C(O)OR_{52}$, $-OC(O)R_{53}$, $-S(O)_2R_{54}$, $-S(O)_2OR_{55}$, $-OS(O)_2R_{56}$, and $-P(O)(OR_{57})(OR_{58})$;

or when two or more substituents selected from R_f are present on the same group, the two substituents, together with the atom linked thereto, may form the following groups unsubstituted or optionally substituted with 1, 2, or more R_g: C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, and 3- to 20-membered heterocyclyl;

R_g are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, and R_{58} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2;

the 3- to 20-membered heterocyclyl represents a saturated or unsaturated non-aromatic ring or ring system; for example, it is a 4-, 5-, 6-, or 7-membered monocyclic ring system, a 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic (e.g., fused, bridged, or spiro) ring system, or a 10-, 11-, 12-, 13-, 14-, or 15-membered tricyclic ring system, and contains at least one, e.g., 1, 2, 3, 4, 5, or more heteroatoms independently selected from O, S, and N, wherein N and S may also be optionally oxidized to various oxidized forms to form nitrogen oxides, -S(O)-, or $-S(O)_2-$;

the C_{6-20} aryl represents an aromatic or partially aromatic monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic hydrocarbon ring having 6-20 carbon atoms, which may be a single aromatic ring or multiple aromatic rings fused together;

the 5- to 20-membered heteroaryl represents a monovalent monocyclic, bicyclic (e.g., fused, bridged, or spiro) or tricyclic aromatic ring system, wherein the aromatic ring system has 5-20 ring atoms and contains 1, 2, 3, 4, 5, or more heteroatoms independently selected from N, O, and S.

According to an embodiment of the present disclosure, L represents alkynyl, a mono- or

polycyclic C_{6-20} aryl group, or mono- or polycyclic C_{6-20} aryl-fused 4- to 7-membered cycloalkyl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of fluorine, chlorine, bromine, hydroxyl, CN, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $NR^{1.2}R^{1.3}$, $CH_2\text{-}NR^{1.2}R^{1.3}$, $CH_2CH_2\text{-}NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{1.1}$, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, $SO_2\text{-}CH_3$, $SO_2\text{-}CH_2CH_3$, and $SO_2\text{-}NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{1.3}$; or

L represents a group selected from a heterocyclic ring and heteroaryl, and is independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, $CH=CHCOOR^{1.1}$, $CO\text{-}NR^{1.1}CH_2CO\text{-}NR^{1.1}$, $CH_2CH_2CO\text{-}NR^{1.1}$, $CH=CHCO\text{-}NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents is optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaryl is 5- to 10-membered monocyclic or bicyclic, optionally fused, heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O; in some embodiments, L is selected from 5-membered monocyclic heteroaryl, a 5-membered heteroaryl-fused phenyl ring, 5-membered heteroaryl-fused 5- to 10-membered heteroaryl, 5-membered heteroaryl-fused 4- to 7-membered cycloalkyl, 5-membered heteroaryl-fused 4- to 7-membered heterocycloalkyl, 6-membered heteroaryl-fused phenyl ring, 6-membered

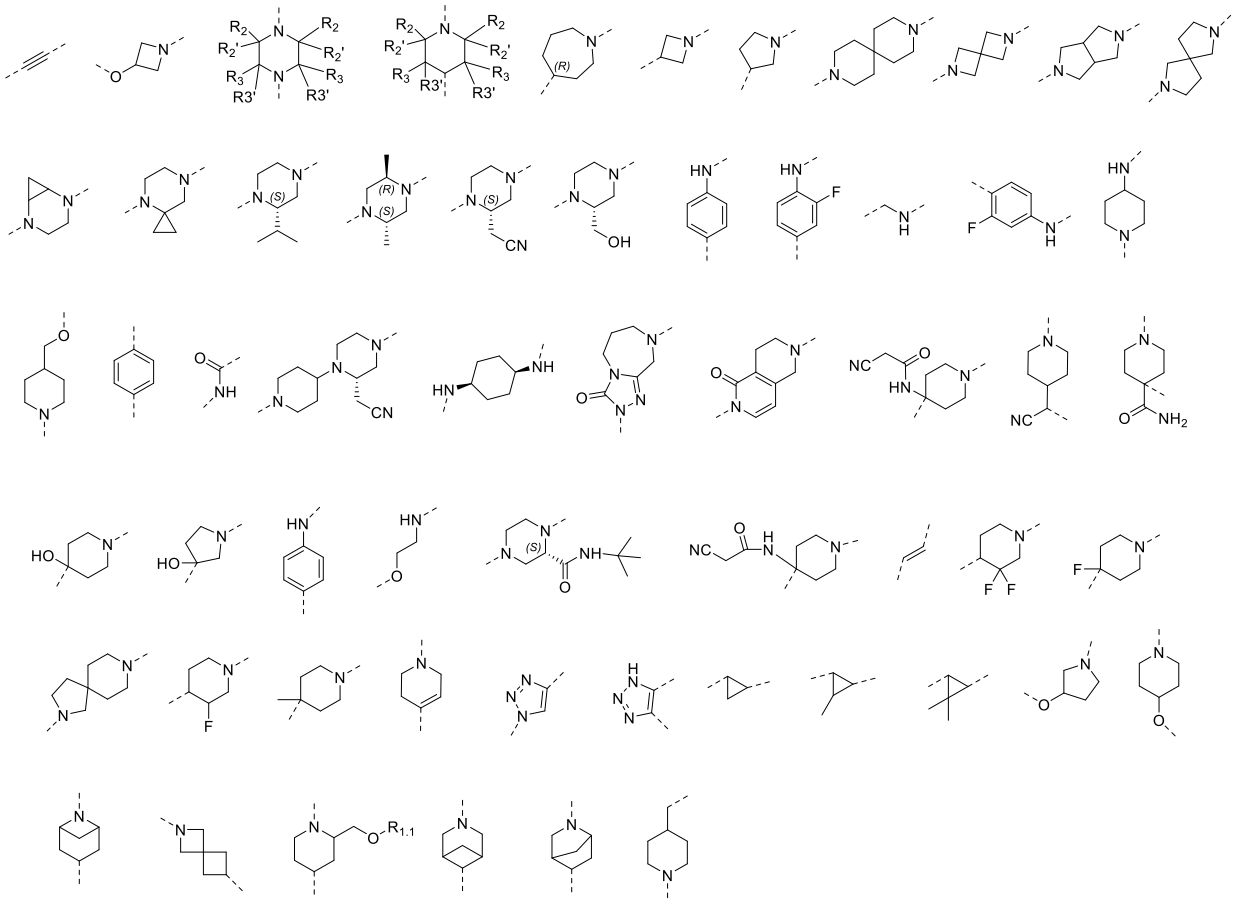
heteroaryl-fused 5- to 10-membered heteroaryl, 6-membered heteroaryl-fused 6-membered heteroaryl, 6-membered heteroaryl-fused 4- to 7-membered cycloalkyl, and 6-membered heteroaryl-fused 4- to 7-membered heterocycloalkyl;

the cycloalkyl may be saturated or partially saturated;

$R^{1.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, C_{3-11} mono- or bicyclic heterocyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{1.2}$ and $R^{1.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{1.1}$, and $COOR^{1.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{1.1}$;

for example, L may be selected from the following groups:



for example, R_{d2} are identical or different, and each independently represent hydrogen, halogen, cyano, hydroxyl, CF_3, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CHF_2, CH_2F, SO_2-CH_3, SO_2-CH_2CH_3, SO_2-$NR^{1.2}R^{1.3}$, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, or C_{1-3} alkyl-$NHR^{1.1}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, $OR^{1.1}$, oxo, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$.

for example, R_e may be selected from OH;

R_{d6} are identical or different, and each independently represent H, F, Me, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{1.1}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, mono- or polycyclic C_{6-20} aryl, mono- or polycyclic C_{6-20} aryl-fused 4- to 7-membered cycloalkyl, mono- or polycyclic C6-20 heteroaryl-fused 4- to 7-membered cycloalkyl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl; or

R_{d6} are identical or different, and each independently represent H, F, Me, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{1.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{1.1}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-6} alkyl, C_{5-10} heteroaryl-C_{1-6} alkyl, a C_{3-10} heterocyclic ring, a C_{5-10} heterocyclic ring, -NR'R'', fluorine, C_{1-6} fluoroalkyl, and C_{1-6} fluoroalkoxy, wherein R' and R'' are independently selected from H and C_{1-6} alkyl; the group, in each case, may be optionally substituted with 1, 2, or more substituents selected from OH, oxo, halogen, C_{1-6} alkyl, and O-C_{1-6} alkyl;

or two R_{d6}, together with the atom linked thereto, form 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged cycloalkyl, or a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, $CH{=}CHCOOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, $CH{=}CHCO$-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.22.3}$;

$R^{2.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents selected from OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{6-20} aryl;

$R^{2.2}$ and $R^{2.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkylene, mono- or bicyclic C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH-CH_3, -CO-$N(CH_3)_2$, SO_2-(C_{1-3} alkyl), CO-$R^{2.1}$, and $COOR^{2.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{2.1}$.

R_c are identical or different, and each independently represent hydrogen, a mono- or polycyclic C_{6-20} aryl group, or mono- or polycyclic C_{6-20} aryl-fused 4- to 7-membered cycloalkyl, for example, C_{4-10} cycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-fused C_{6-20} aryl-, C_{4-10} cycloalkyl-C_{6-20} aryl-, 4-

to 10-membered heterocycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl, C_{4-10} cycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-fused 5- to 20-membered heteroaryl-, C_{4-10} cycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-5- to 20-membered heteroaryl-, or 4- to 10-membered heterocycloalkenyl-5- to 20-membered heteroaryl-, or are selected from 5- to 20-membered heteroaryl-O-C_{6-20} aryl-, 5- to 20-membered heteroaryl-N-C_{6-20} aryl-, 5- to 20-membered heteroaryl-S-C_{6-20} aryl-, and 5- to 20-membered heteroaryl-CH_2-C_{6-20} aryl-, wherein the above groups may be each independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituent of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{4.1}$, $COOR^{4.1}$ $CH_2COOR^{4.1}$, $CH_2CH_2COOR^{4.1}$, $CH{=}CHCOOR^{4.1}$, $CO\text{-}NR^{4.1}$ $CH_2CO\text{-}NR^{4.1}$, $CH_2CH_2CO\text{-}NR^{4.1}$, $CH{=}CHCO\text{-}NR^{4.1}$, $NR^{4.2}R^{4.3}$, $CH_2\text{-}NR^{4.2}R^{4.3}$, $CH_2CH_2\text{-}NR^{4.2}R^{4.3}$, C_{1-3} alkyl-CN, C_{1-3} alkyl-OH, C_{1-3} alkyl-$OR^{4.1}$, C_{1-3} alkyl-NH_2, C_{1-3} alkyl-$NHR^{4.1}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{4.2}R^{4.3}$;

or R_c are identical or different, and each independently represent a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{4.1}$, C_{1-3} alkyl-$OR^{4.1}$, $SR^{4.1}$, C_{1-3} alkyl-$SR^{4.1}$, $SO\text{-}R^{4.1}$, C_{1-3} alkyl-$SOR^{4.1}$, $SO_2\text{-}R^{4.1}$, C_{1-3} alkyl-$SO_2R^{4.1}$, $COOR^{4.1}$, $CH_2COOR^{4.1}$, $CH_2CH_2COOR^{4.1}$, $CH{=}CHCOOR^{4.1}$, $CO\text{-}NR^{4.1}$ $CH_2CO\text{-}NR^{4.1}$, $CH_2CH_2CO\text{-}NR^{4.1}$, $CH{=}CHCO\text{-}NR^{4.1}$, $COR^{4.1}$, $CH_2COR^{4.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 10-membered heterocyclyl-C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{4.1}$, and $NR^{4.2}R^{4.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{4.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{4.2}R^{4.3}$;

the heterocyclic ring represents a 3- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O;

the heteroaromatic ring is 5- to 10-membered monocyclic or bicyclic, optionally fused,

heteroaryl that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O; in some embodiments, R_4 is selected from 5-membered monocyclic heteroaryl, a 5-membered heteroaryl-fused phenyl ring, 5-membered heteroaryl-fused 5- to 10-membered heteroaryl, 5-membered heteroaryl-fused 4- to 7-membered cycloalkyl, 5-membered heteroaryl-fused 4- to 7-membered heterocycloalkyl, 6-membered heteroaryl-fused phenyl ring, 6-membered heteroaryl-fused 5- to 10-membered heteroaryl, 6-membered heteroaryl-fused 6-membered heteroaryl, 6-membered heteroaryl-fused 47-membered cycloalkyl, and 6-membered heteroaryl-fused 4- to 7-membered heterocycloalkyl;

the cycloalkyl may be saturated or partially saturated;

$R^{4.1}$ is H or a group selected from C_{1-6} alkyl, C_{1-6} alkyl alcohol, C_{1-3} haloalkyl, a mono- or bicyclic ring, -C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, 3- to 10-membered heterocyclic-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, 5- to 20-membered heteroaryl, and a heterocyclic ring, which may be optionally substituted with substituents of OH, O-(C_{1-3} alkyl), halogen, C_{1-10} alkyl, and C_{5-10} aryl;

$R^{4.2}$ and $R^{4.3}$ each independently represent H or a group selected from C_{1-6} alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, mono- or bicyclic C_{6-20} aryl, a 3- to 10-membered heterocyclic ring, a heteroaromatic ring, CO-NH_2, CO-NH.CH_3, -CO-N(CH_3)$_2$, SO_2-(C_{1-3} alkyl), CO-$R^{4.1}$, and $COOR^{4.1}$, which may be optionally substituted with 1, 2, or more substituents selected from OH, halogen, C_{1-6} alkyl, C_{6-20} aryl, and $COOR^{4.1}$;

for example, the 4- to 10-membered heterocyclyl or 4- to 10-membered heterocycloalkenyl may be: 1-methylpyrrolidinyl, 1-ethylpyrrolidinyl, 1-cyclopropylpyrrolidinyl, 1-cyclopropylmethylpyrrolidinyl, 5-methyl-4,5-dihydropyridazin-3(2H)-one, 1-methylazetidinyl, or 1-methylpiperidinyl.

12. The compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to any one of claims 1-11, wherein:

R_1 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3}-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, $COOR^{1.1}CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=$CHCOOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$,

CH=CHCO-$NR^{1.1}$, $NR^{1.2}R^{1.3}$, CH_2-$NR^{1.2}R^{1.3}$, CH_2CH_2-$NR^{1.2}R^{1.3}$, C_{3-10} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-20} aryl, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{1.2}R^{1.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, CN, C_{1-3} alkyl-CN, -SH, $-NH_2$, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3} alkyl-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, $-OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$, wherein $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$ have the definitions described above; or,

R_1 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, CN, NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, nitro, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{1.1}$, C_{1-3} alkyl-$OR^{1.1}$, $SR^{1.1}$, C_{1-3} alkyl-$SR^{1.1}$, SO-$R^{1.1}$, C_{1-3} alkyl-$SOR^{1.1}$, SO_2-$R^{1.1}$, C_{1-3} alkyl-$SO_2R^{1.1}$, $COOR^{1.1}$, $CH_2COOR^{1.1}$, $CH_2CH_2COOR^{1.1}$, CH=CH$COOR^{1.1}$, CO-$NR^{1.1}CH_2$CO-$NR^{1.1}$, CH_2CH_2CO-$NR^{1.1}$, CH=CHCO-$NR^{1.1}$, $COR^{1.1}$, $CH_2COR^{1.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{1.1}$, and $NR^{1.2}R^{1.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, CN, C_{1-3} alkyl-CN, -SH, $-NH_2$, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3} alkyl-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$, wherein $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$ have the definitions described above; or,

R_2 represents hydrogen or a mono- or polycyclic C_{6-20} aryl group, and may be independently and optionally substituted at any of the ortho-, para-, and meta-positions with one, two, or three substituents of fluorine, chlorine, bromine, iodine, hydroxyl, CN, NO_2, and NH_2, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $C(CH_3)_2COOR^{2.1}$, $CF_2COOR^{2.1}$, $CHFCOOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}$, CH_2CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $NR^{2.2}R^{2.3}$, CH_2-$NR^{2.2}R^{2.3}$, CH_2CH_2-$NR^{2.2}R^{2.3}$, C_{3-10}

cycloalkyl, $COOR^{2.1}$-C_{3-8} cycloalkyl, CO-$NR^{2.1}$-C_{3-8} cycloalkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, C_{1-6} alkyl, C_{1-3} fluoroalkyl, CF_3, CHF_2, CH_2F, C_{6-20} aryl-C_{1-6} alkyl, 3- to 20-membered heterocyclic-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{6-10} aryl, C_{1-3} alkyl-$SOR^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, SO_2-CH_3, SO_2-CH_2CH_3, and SO_2-$NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, CN, C_{1-3} alkyl-CN, -SH, $-NH_2$, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3}-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$, wherein $R^{2.1}$, $R^{2.2}$, and $R^{2.3}$ have the definition described above; or,

R_2 represents a group selected from a heterocyclic ring and heteroaryl, and may be independently and optionally substituted at the ortho-, para-, or meta-position with one, two, or three groups of halogen, OH, CN, NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, nitro, oxo, CF_3, CHF_2, and CH_2F, or substituted with 1, 2, or more substituents selected from $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $COOR^{2.1}$-C_{3-8} cycloalkyl, CO-$NR^{2.1}$-C_{3-8} cycloalkyl, $CH_2CH_2COOR^{2.1}$, CH=CH$COOR^{2.1}$, CO-$NR^{2.1}CH_2CO$-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic-C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be optionally substituted with 1, 2, or more substituents of OH, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$, wherein $R^{2.1}$, $R^{2.2}$, and $R^{2.3}$ have the definitions described above; or

R_2 and $R_{2'}$, together with the atom linked thereto, form a 4- to 11-membered, monocyclic or bicyclic, saturated or partially saturated, optionally fused or optionally bridged heterocyclic ring that contains 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, wherein the heterocyclic ring is unsubstituted or optionally substituted at the ortho-, para-, or meta-position with 1, 2, or more substituents selected from: halogen, OH, oxo, CF_3, CHF_2, CH_2F, $OR^{2.1}$, C_{1-3} alkyl-$OR^{2.1}$, C_{1-3} alkyl-O-C_{1-3} alkyl-COOH, C_{1-3} alkyl-O-C_{1-3} alkyl-$CONR^{2.1}$, C_{1-3} alkyl-phosphoric acid, C_{1-3} alkyl-O-C(O)-$OR^{2.1}$, C_{1-3} alkyl-O-C(O)-$NR^{2.1}$, C_{1-3} alkyl-O-C(=O)-C_{1-3} alkyl-(O-C_{1-3} alkyl)v, C_{1-3} alkyl-O-C(=O)-C_{1-6} alkyl-$COOR^{2.1}$, C_{1-3} alkyl-N-C(=O)-C_{1-6}

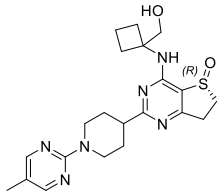
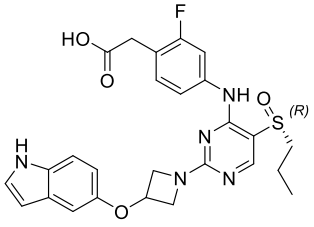
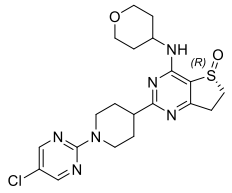
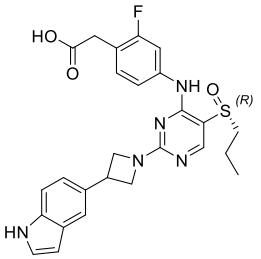
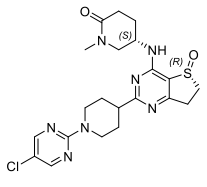
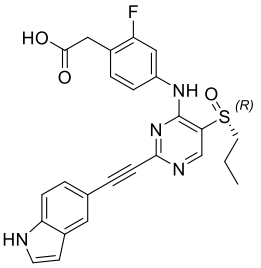
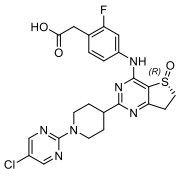
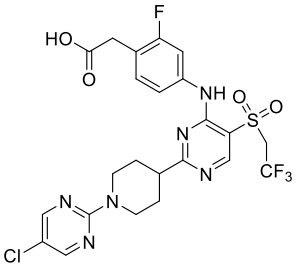
alkyl-$COOR^{2.1}$, C_{1-3} alkyl-N-C(=O)-C_{1-6} alkyl-$COOR^{2.1}$, C_{1-3} alkyl-N-C(=O)-N-C_{1-6} alkyl-$COOR^{2.1}$, $SR^{2.1}$, C_{1-3} alkyl-$SR^{2.1}$, SO-$R^{2.1}$, C_{1-3} alkyl-$SOR^{2.1}$, SO_2-$R^{2.1}$, C_{1-3} alkyl-$SO_2R^{2.1}$, $COOR^{2.1}$, $CH_2COOR^{2.1}$, $CH_2CH_2COOR^{2.1}$, CH=$CHCOOR^{2.1}$, CO-$NR^{2.1}$, CH_2CO-$NR^{2.1}$, CH_2CH_2CO-$NR^{2.1}$, CH=CHCO-$NR^{2.1}$, $COR^{2.1}$, $CH_2COR^{2.1}$, C_{1-6} alkyl alcohol, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-20} aryl, C_{1-6} alkyl, C_{6-20} aryl-C_{1-6} alkyl, 5- to 20-membered heteroaryl-C_{1-6} alkyl, C_{1-3} alkyl-(monocyclic or polycyclic C_{6-20} aryl), 3- to 20-membered heterocyclyl-C_{6-20} aryl, a 3- to 20-membered heterocyclic ring, 5- to 20-membered heteroaryl C_{1-3} alkyl-$OR^{2.1}$, $NR^{2.2}R^{2.3}$, C_{6-20} aryl, and $NR^{2.2}R^{2.3}$, wherein each of the substituents may be sequentially and optionally substituted with 1, 2, or more substituents selected from OH, CN, C_{1-3} alkyl-CN, C_{1-3} alkyl-NH_2, -SH, -NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3} alkyl-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, -$OR^{1.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-20} aryl, and $NR^{1.2}R^{1.3}$, wherein $R^{2.1}$, $R^{1.2}$, $R^{1.3}$, and v have the definitions described above; or,

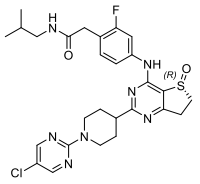
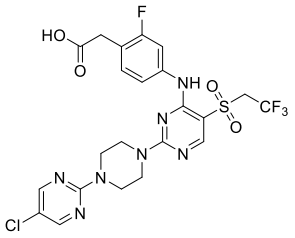
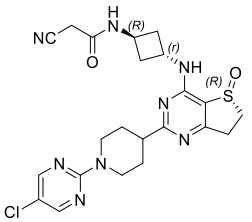
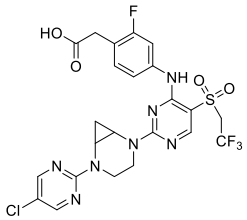
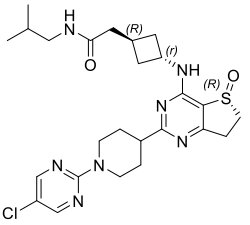
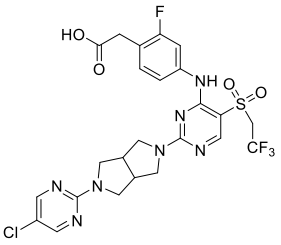
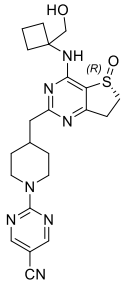
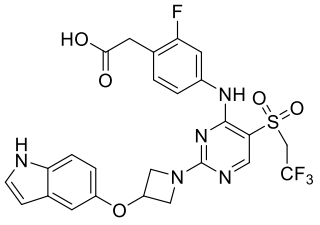
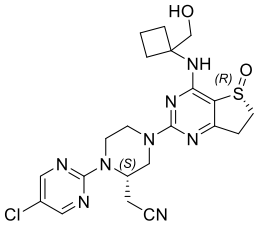
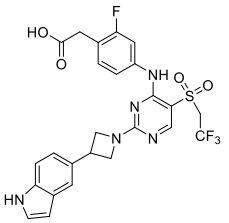
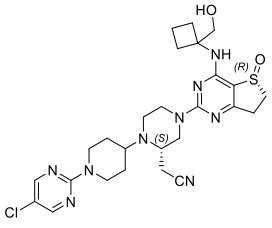
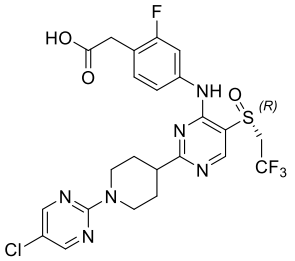
R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, and R_{58} are each identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, 5- to 20-membered heteroaryl, 3- to 20-membered heterocyclyl, and NH_2, wherein each of the above groups may be optionally substituted with 1, 2, or more substituents of OH, CN, C_{1-3} alkyl-CN, -SH, -NH_2, -NHOH, -C_{1-3} alkyl-NHOH, -C_{1-3} alkyl-CO-NHOH, -CO-NHOH, -C_{1-3} alkyl-NH-CO-$NR^{1.2}R^{1.3}$, -$NR^{1.1}$CN, -CHO, C_{2-6} alkenyl, -O-C_{3-8} cycloalkyl, $COOR^{1.1}$, C_{1-3} alkyl-$COOR^{1.1}$, $CONHR^{1.1}$, C_{1-3} alkyl-$CONHR^{1.1}$, $OR^{2.1}$, oxo, halogen, CF_3, CHF_2, CH_2F, C_{1-6} alkyl, C_{6-10} aryl, and $NR^{1.2}R^{2.3}$, wherein $R^{1.1}$, $R^{1.2}$, $R^{2.1}$, and $R^{2.3}$ have the definitions above; or,

R_c are identical or different, and are each independently selected from H, halogen, OH, CN, NO_2, oxo (=O), thio (=S), and the following groups unsubstituted or optionally substituted with 1, 2, or more R_e: C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{3-20} cycloalkyl, C_{3-20} cycloalkenyl, C_{3-20} cycloalkynyl, C_{6-20} aryl, C_{1-6} alkyl-C_{4-10} heterocycloalkyl, C_{1-6} alkyl-C_{4-10} heterocycloalkenyl, C_{1-6} alkyl-C_{6-20} aryl, C_{1-6} alkyl-C_{5-20} heteroaryl, 5- to 20-membered heteroaryl-O-C_{6-20} aryl-, 5- to 20-membered heteroaryl-N-C_{6-20} aryl-, 5- to 20-membered heteroaryl-S-C_{6-20} aryl-, 5- to 20-membered heteroaryl-CH_2-C_{6-20} aryl-, C_{4-10} cycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-fused C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-fused C_{6-20} aryl-, C_{4-10} cycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkyl-C_{6-20} aryl-, 4- to 10-membered heterocycloalkenyl-C_{6-20} aryl-, 5- to 20-membered heteroaryl, C_{4-10} cycloalkyl-fused 5- to 20-

membered heteroaryl-, 4- to 10-membered heterocycloalkyl-fused 5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-fused 5- to 20-membered heteroaryl-, C_{4-10} cycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkyl-5- to 20-membered heteroaryl-, 4- to 10-membered heterocycloalkenyl-5- to 20-membered heteroaryl-, 3- to 20-membered heterocyclyl, C_{1-20} alkyloxy, C_{2-20} alkenyloxy, C_{2-20} alkynyloxy, C_{3-20} cycloalkyloxy, C_{3-20} cycloalkenyloxy, C_{3-20} cycloalkynyloxy, C_{6-20} aryloxy, 5- to 20-membered heteroaryloxy, 3- to 20-membered heterocyclyloxy, C_{1-20} alkylthio, C_{2-20} alkenylthio, C_{2-20} alkynylthio, C_{3-20} cycloalkylthio, C_{3-20} cycloalkenylthio, C_{3-20} cycloalkynylthio, C_{6-20} arylthio, 5- to 20-membered heteroarylthio, 3- to 20-membered heterocyclylthio, NH_2, $-C(O)R_{31}$, $-C(O)OR_{32}$, $-OC(O)R_{33}$, $-S(O)_2R_{34}$, $-S(O)_2OR_{35}$, $-OS(O)_2R_{36}$, and $-P(O)(OR_{37})(OR_{38})$, wherein R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, and R_{38} have the definitions described above; or,

the compound is selected from the following compounds:

No.	Chemical Structure	No.	Chemical Structure
002		264	
003		265	
004		266	
005		267	

No.	Chemical Structure	No.	Chemical Structure
006		268	
007		269	
008		270	
009		271	
010		272	
011		273	

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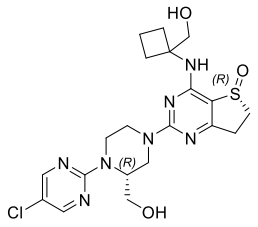
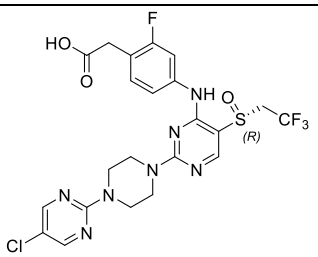
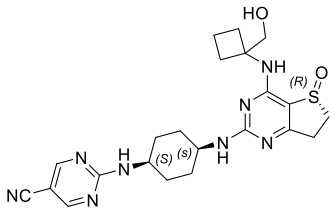
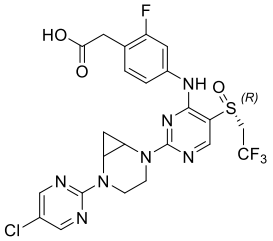
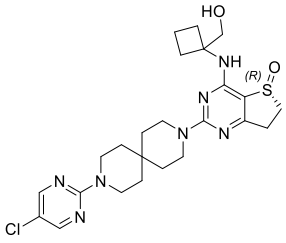
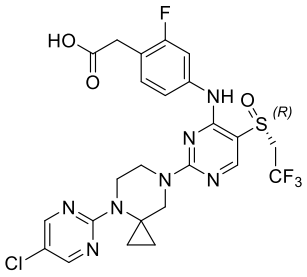
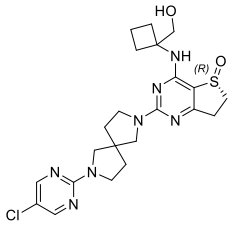
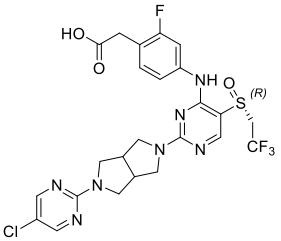
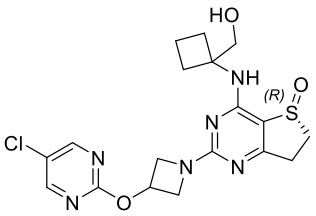
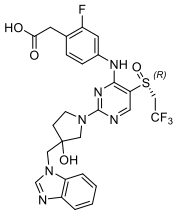
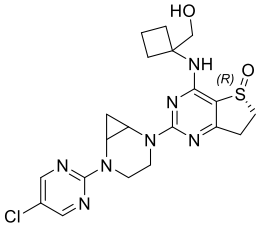
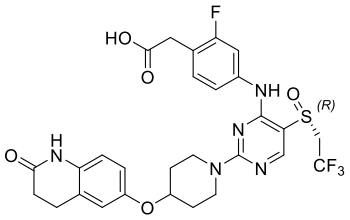
012		274	
013		275	
014		276	
017		277	
019		278	
020		279	

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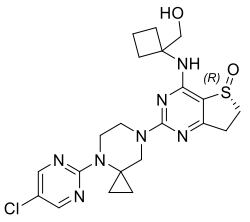
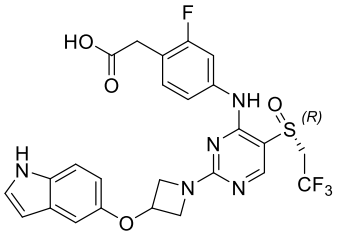
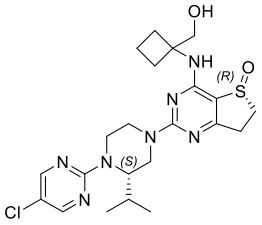
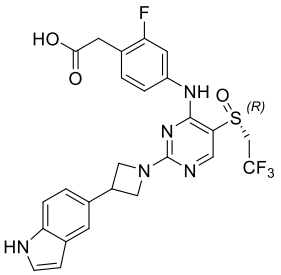
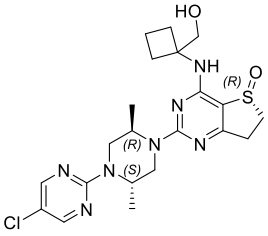
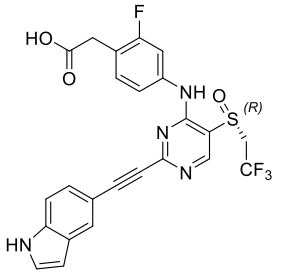
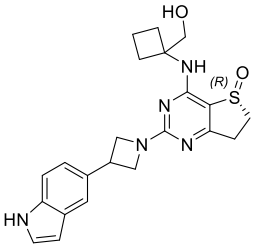
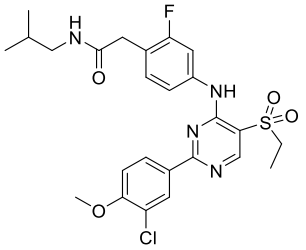
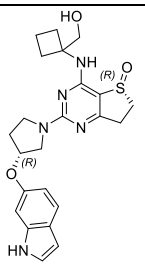
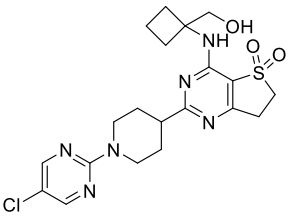
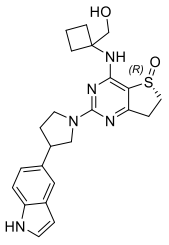
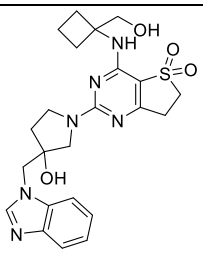
021		280	
022		281	
023		282	
024		283	
025		284	
026		285	

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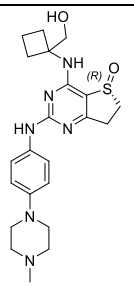
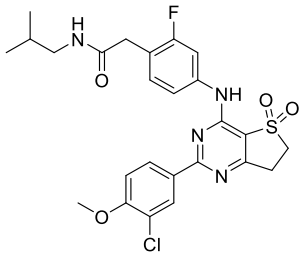
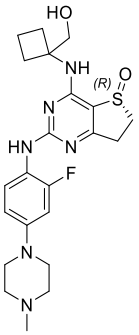
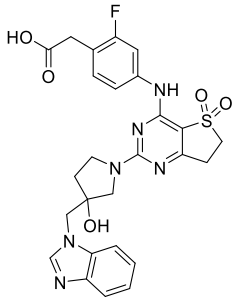
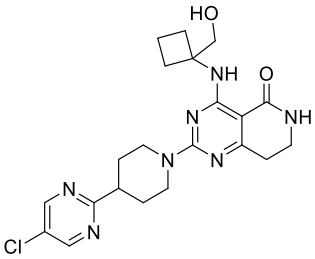
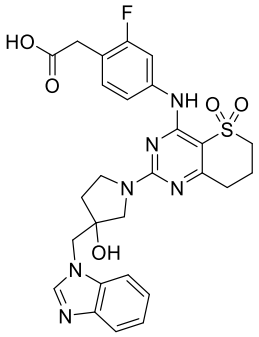
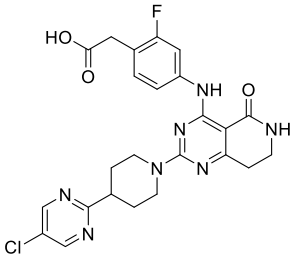
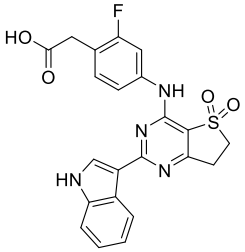
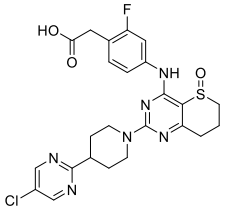
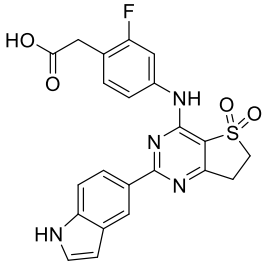
027		286	
028		287	
029		288	
030		289	
032		290	

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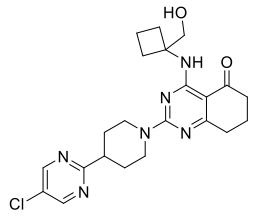
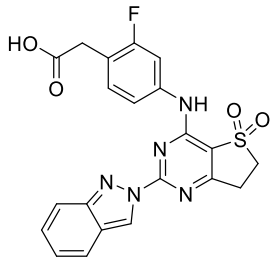
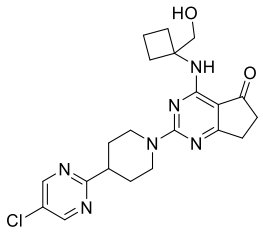
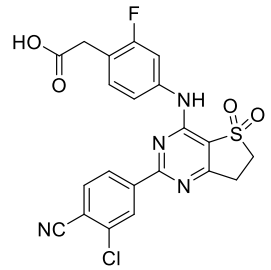
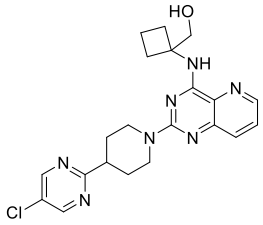
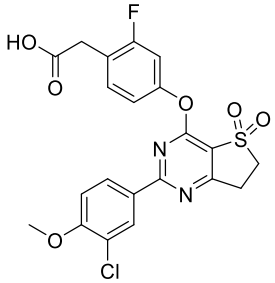
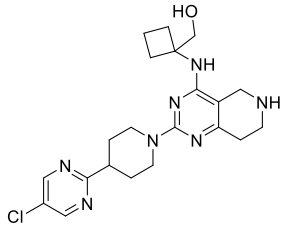
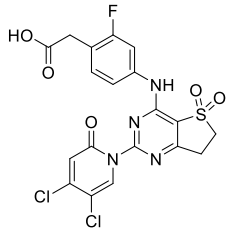
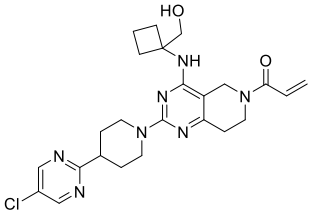
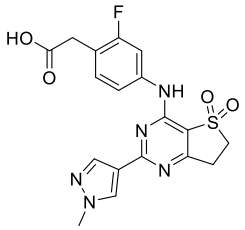
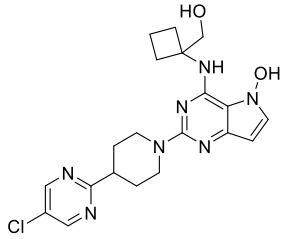
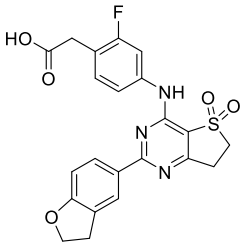
033		291	
034		292	
035		293	
036		294	
037		295	
038		296	

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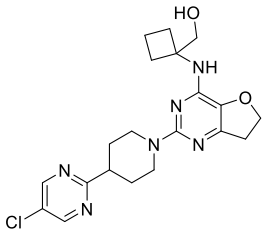
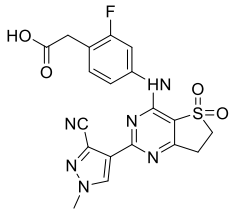
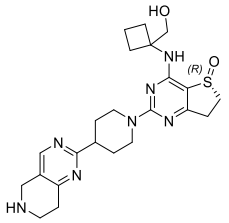
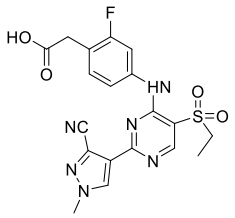
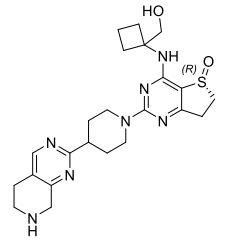
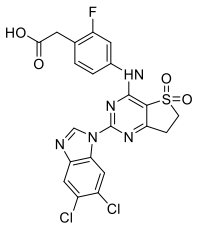
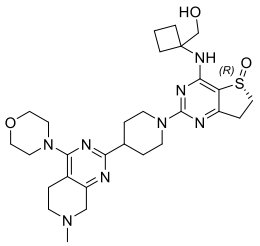
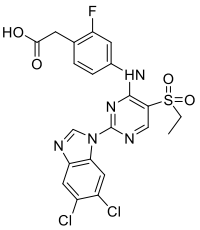
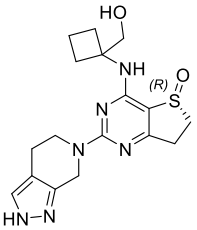
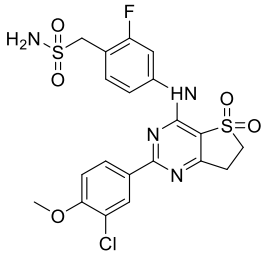
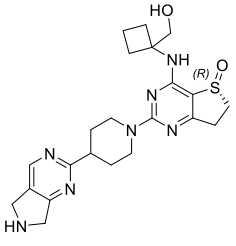
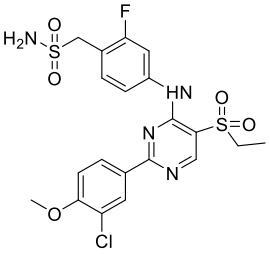
039		297	
040		298	
041		299	
042		300	
043		307	
044		308	

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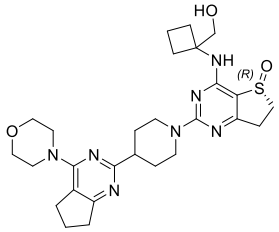
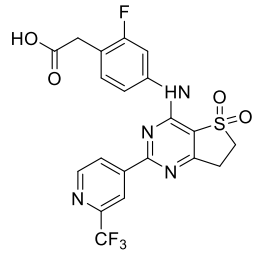
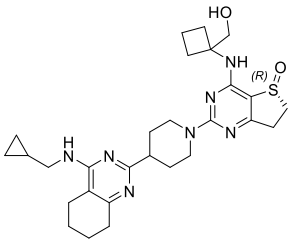
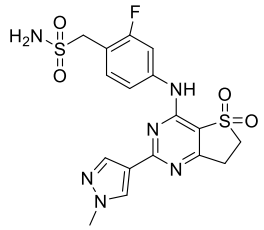
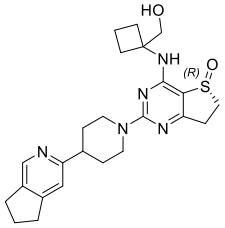
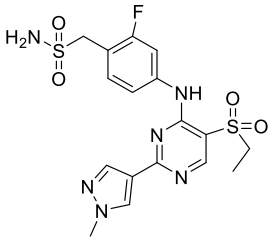
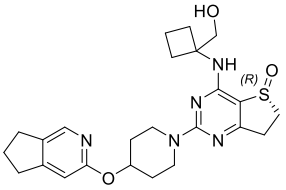
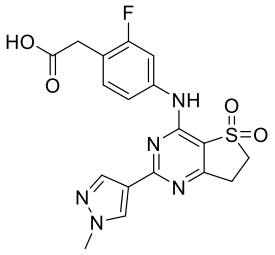
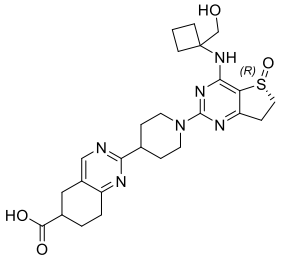
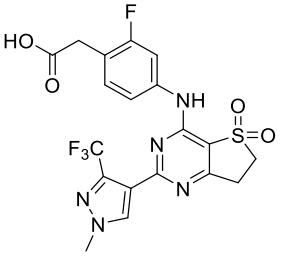
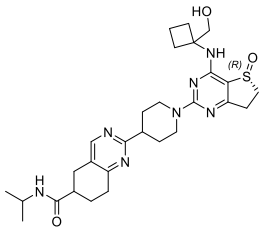
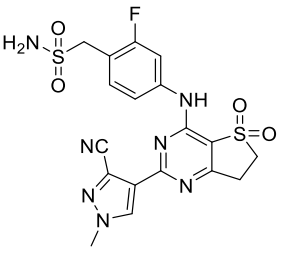
045		311	
046		313	
047		314	
048		315	
049		317	
050		319	

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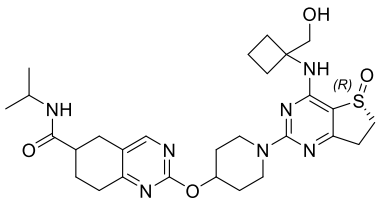
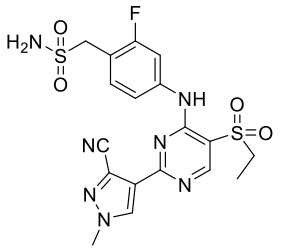
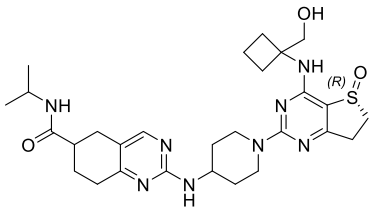
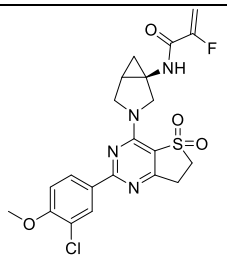
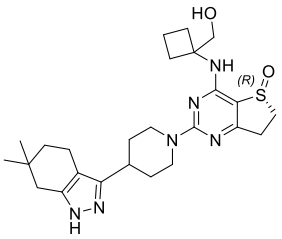
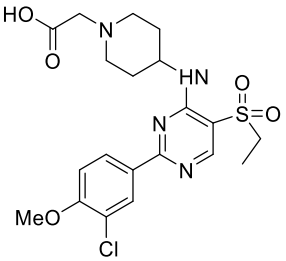
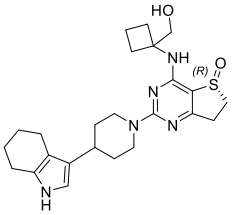
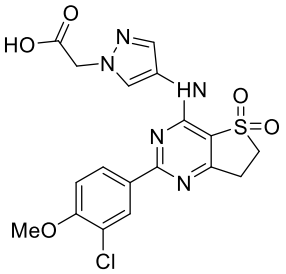
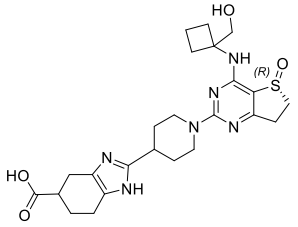
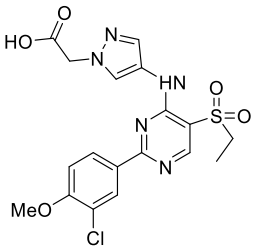
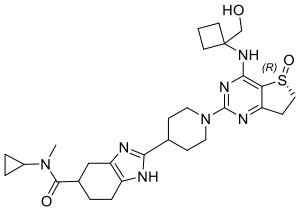
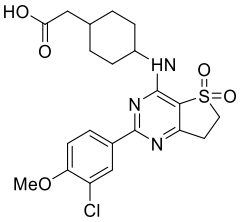
051		320	
052		346	
053		347	
054		349	
055		350	
056		351	

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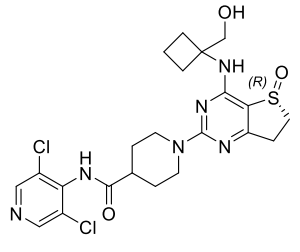
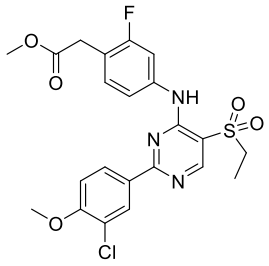
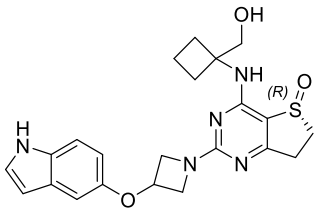
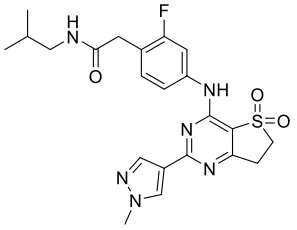
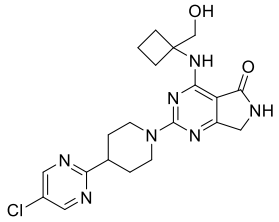
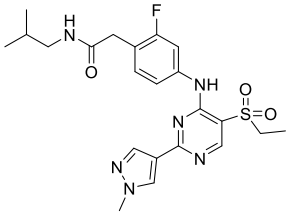
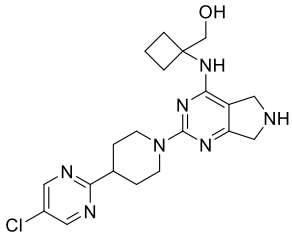
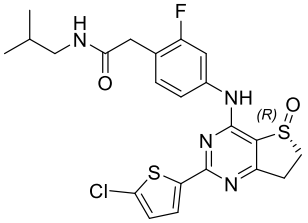
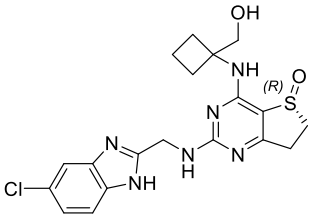
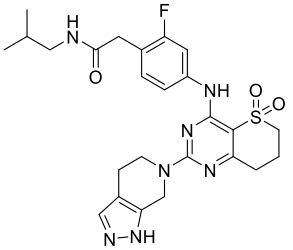
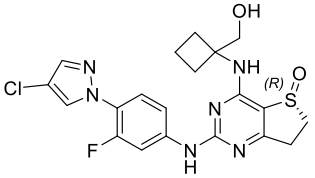
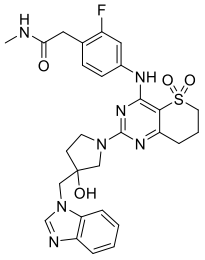
057		352	
058		353	
059		354	
060		355	
061		356	
062		357	

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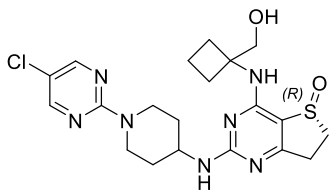
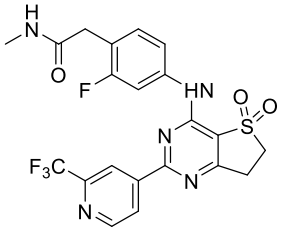
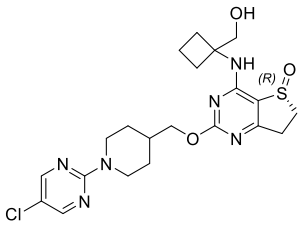
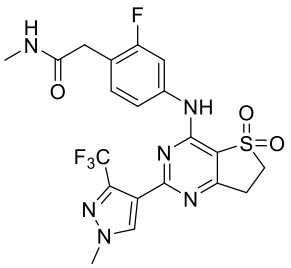
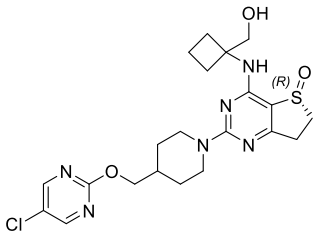
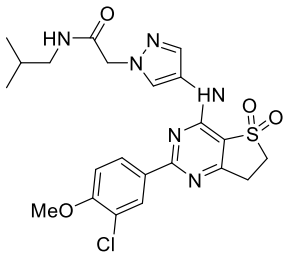
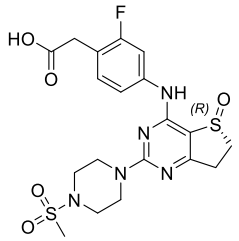
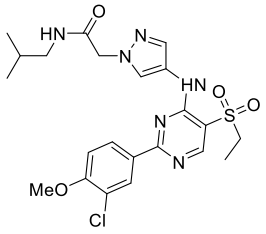
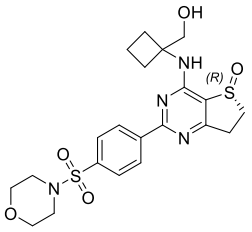
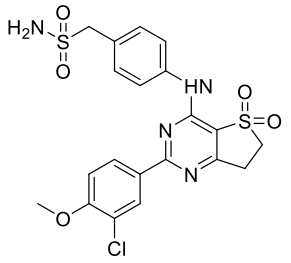
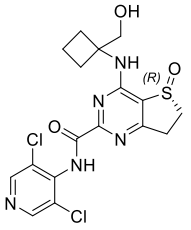
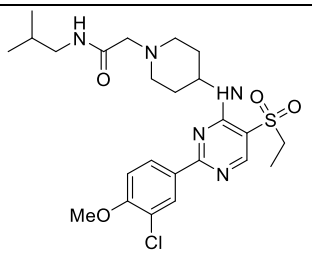
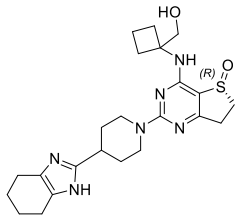
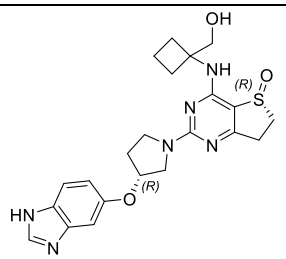
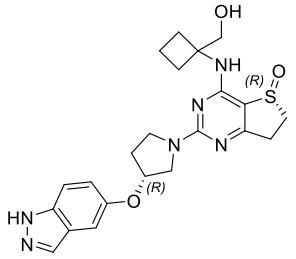
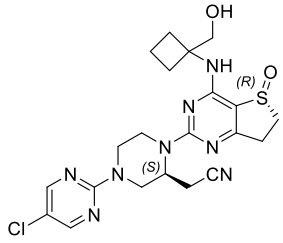
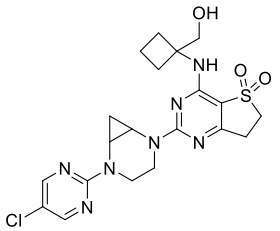
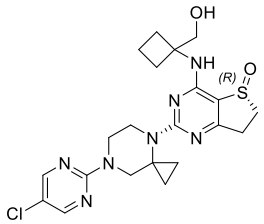
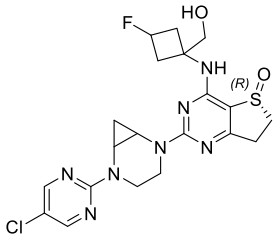
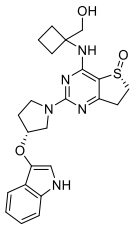
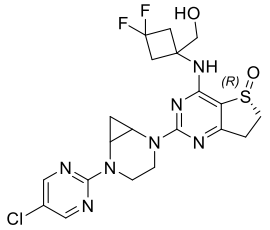
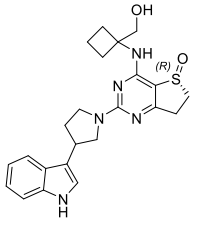
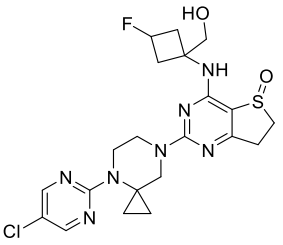
063		358	
064		359	
065		360	
066		361	
067		362	
068		363	

No.	Chemical Structure	No.	Chemical Structure
069		365	
		366	
071		367	
072		368	
073		369	
074		370-rac	

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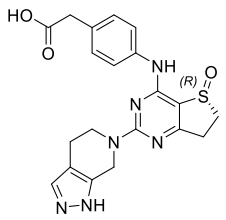
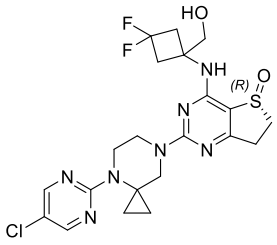
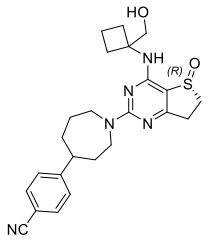
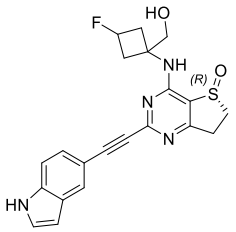
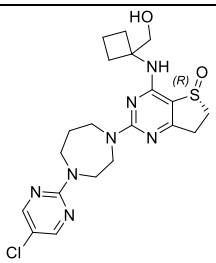
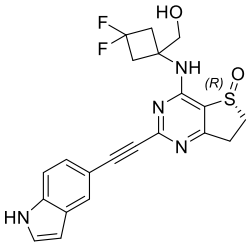
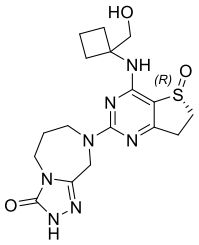
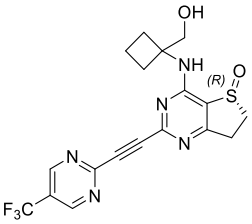
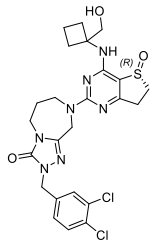
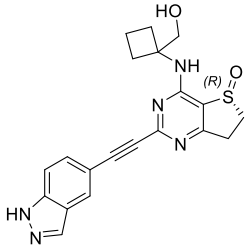
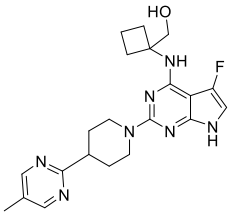
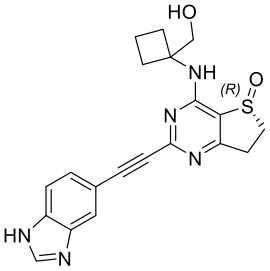
075		371	
076		372	
077		373	
078		374	
079		375	
080		376	

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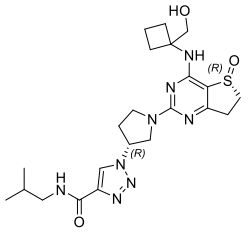
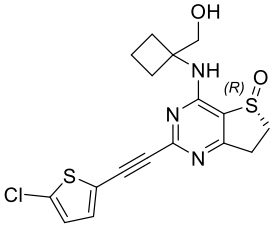
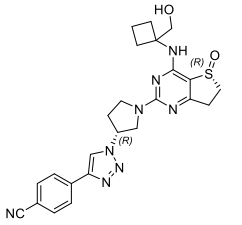
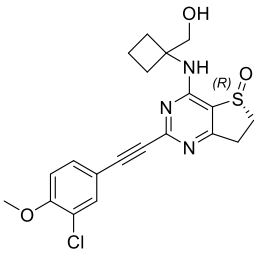
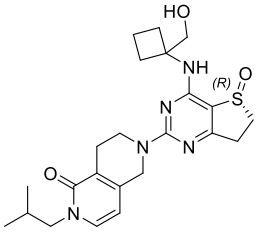
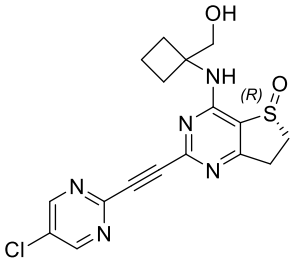
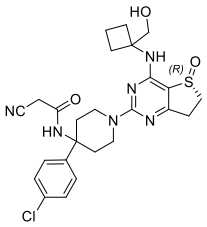
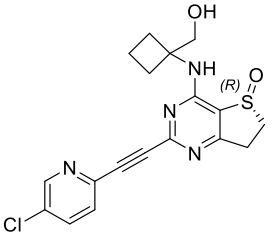
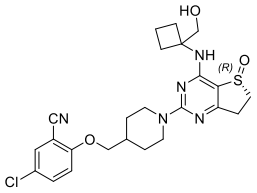
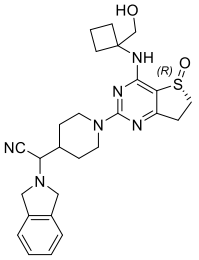
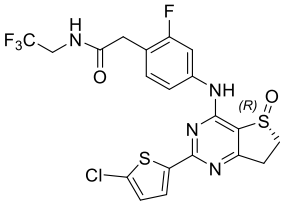
081		377	
082		378	
083		379	
084		380	
085			
086		387	

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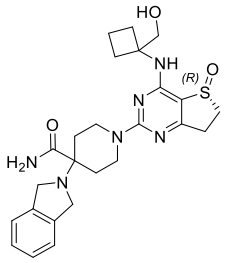
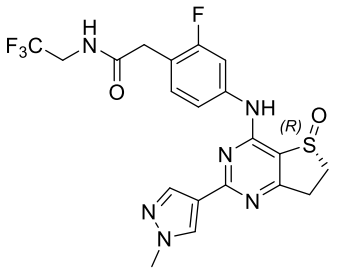
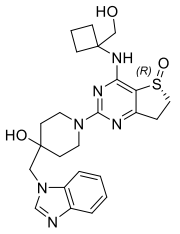
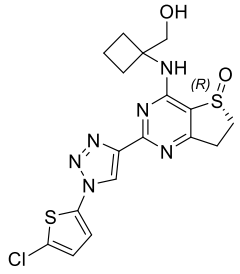
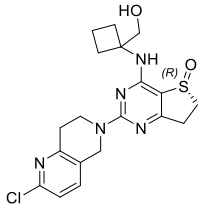
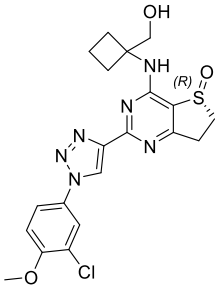
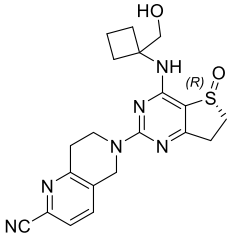
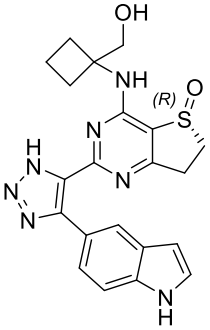
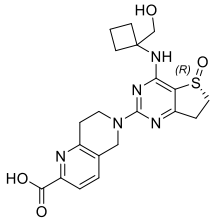
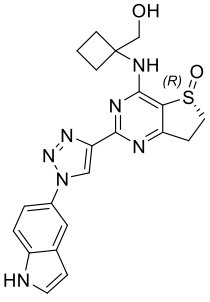
087		398	
088		404	
089		405	
090		406	
091		407	

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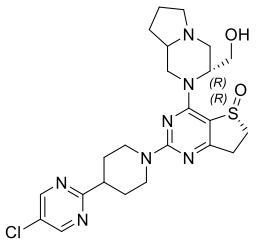
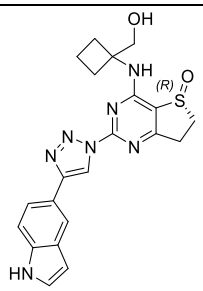
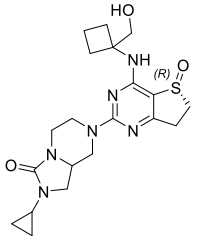
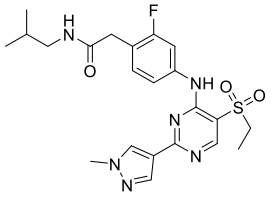
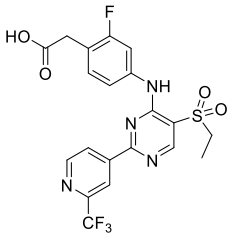
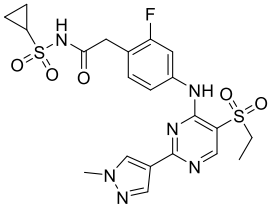
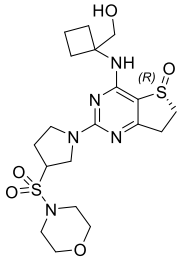
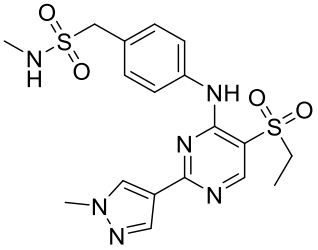
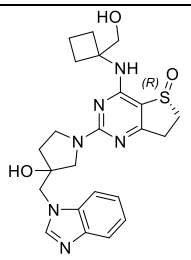
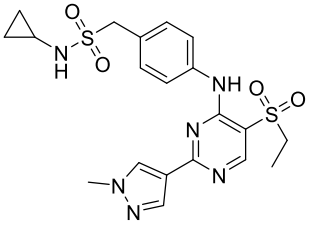
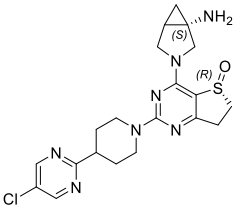
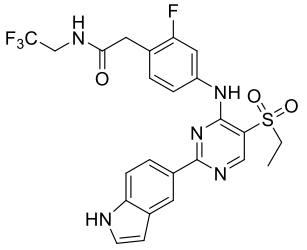
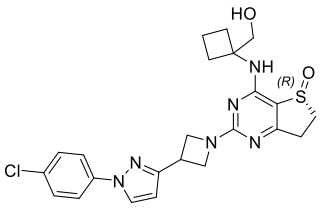
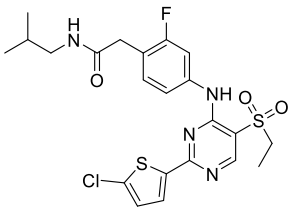
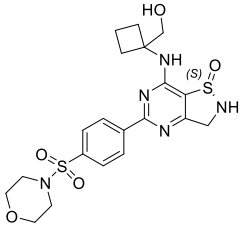
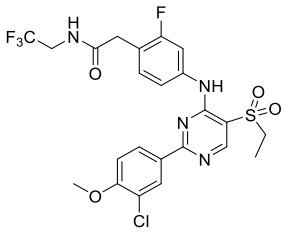
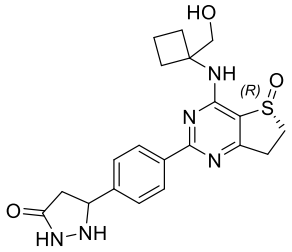
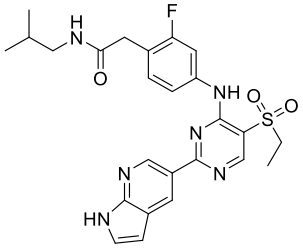
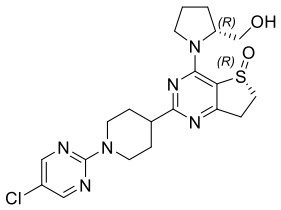
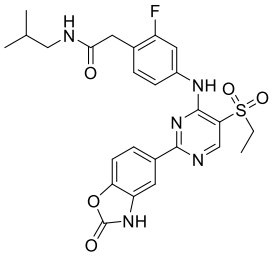
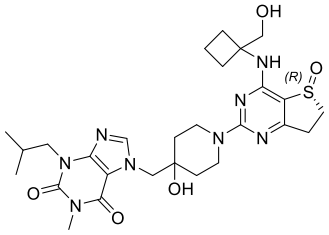
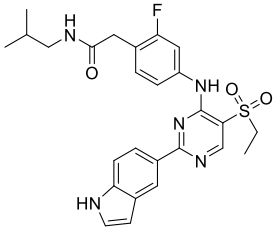
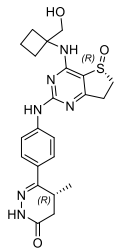
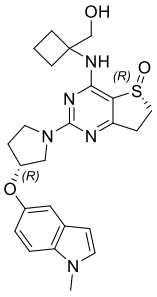
092		408	
093		409	
094		410	
095		411	
096		412	
097		413	

No.	Chemical Structure	No.	Chemical Structure
098		415	
099		416	
100		417	
101		418	
102		419	
103		420	

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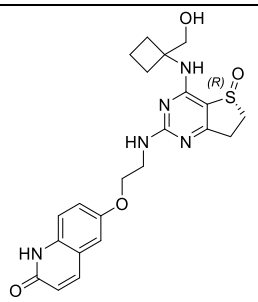
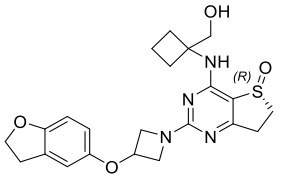
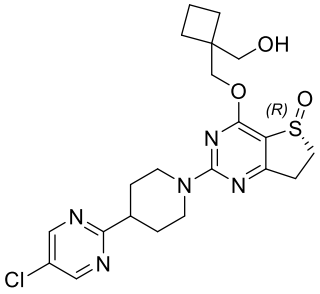
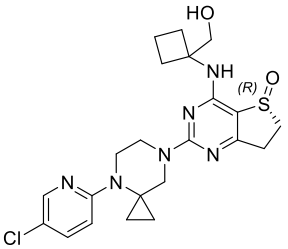
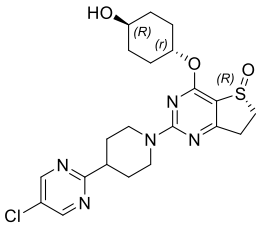
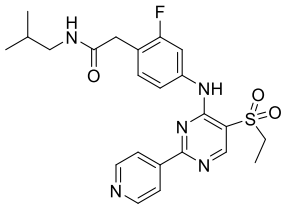
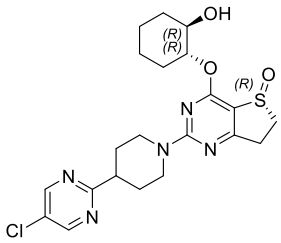
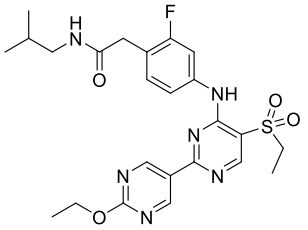
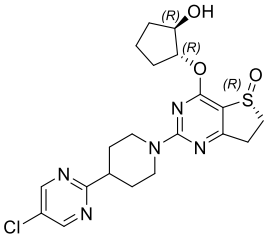
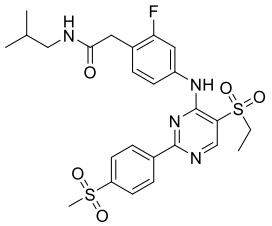
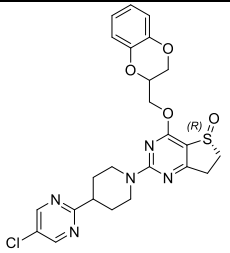
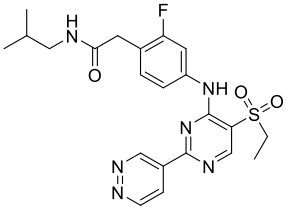
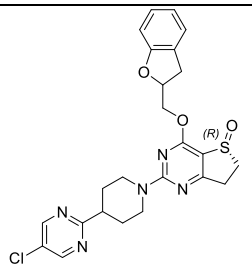
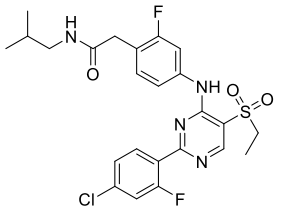
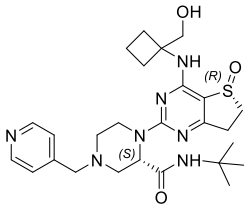
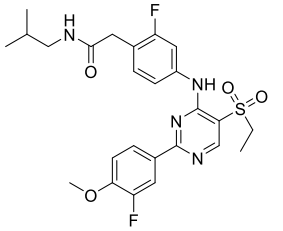
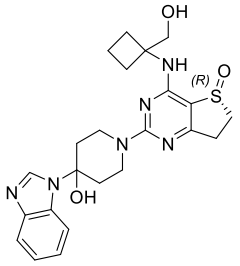
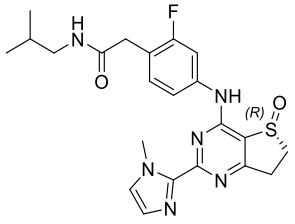
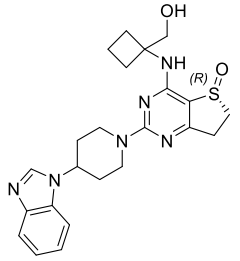
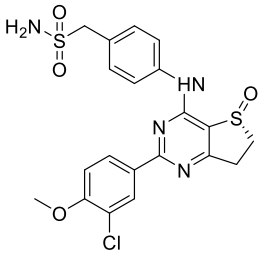
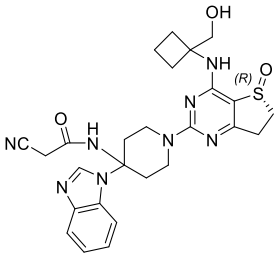
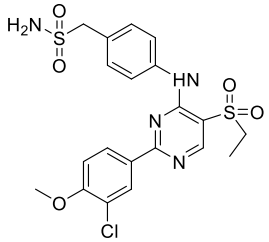
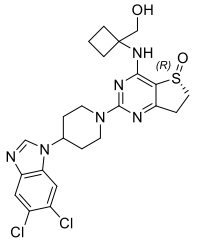
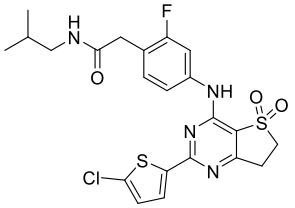
104		421	
105		422	
106		423	
107		424	
108		425	
109		426	

No.	Chemical Structure	No.	Chemical Structure
110		427	
111		428	
112		429	
113		430	
114		431	
115		432	

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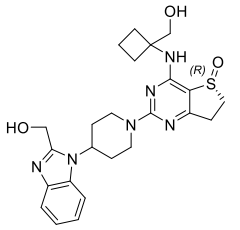
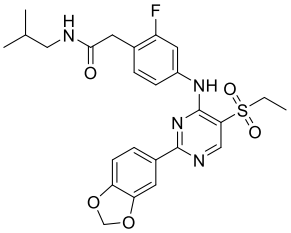
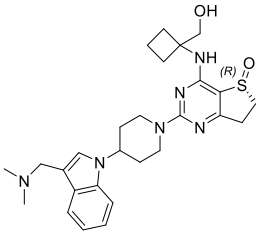
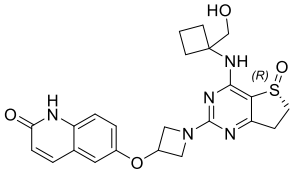
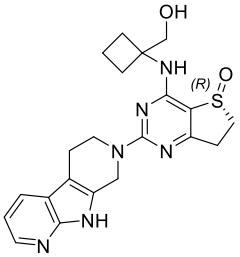
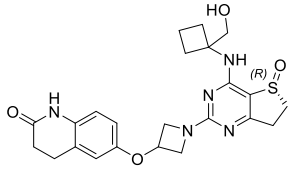
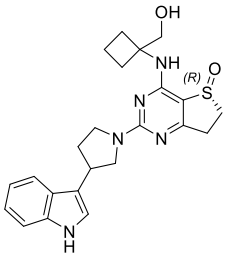
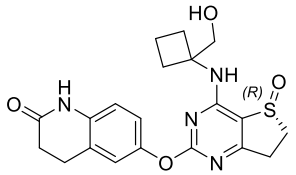
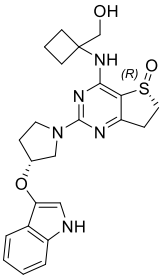
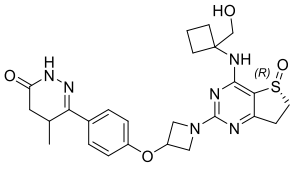
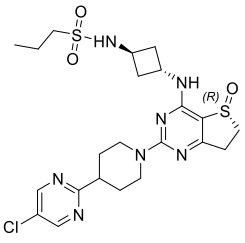
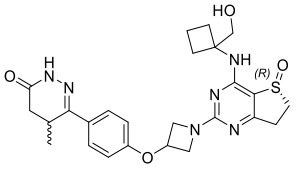
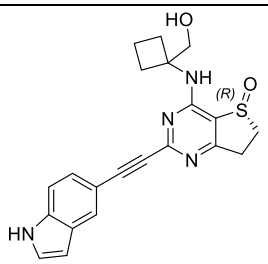
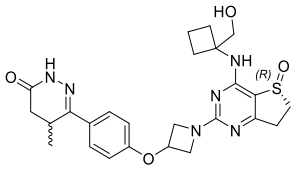
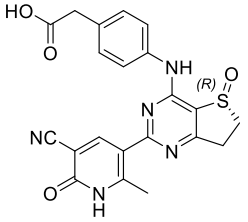
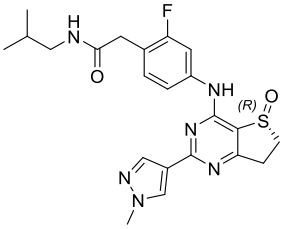
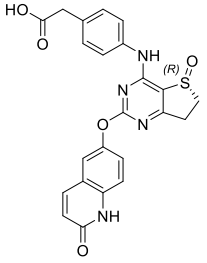
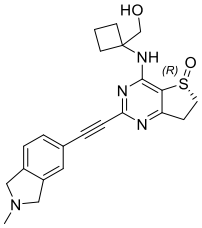
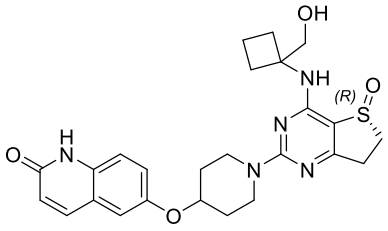
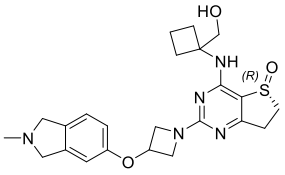
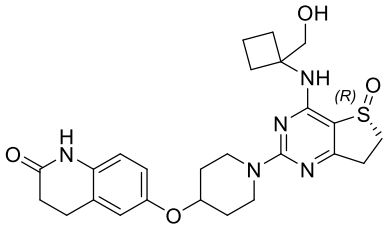
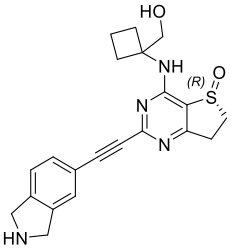
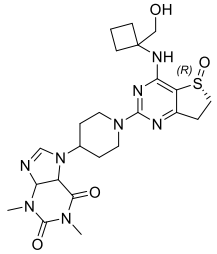
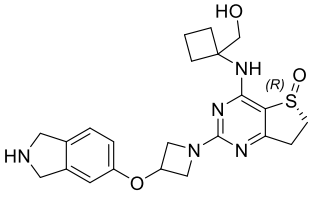
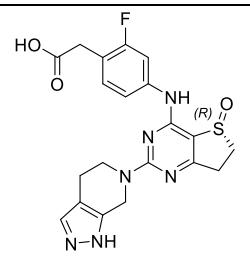
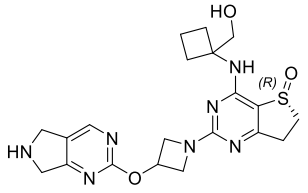
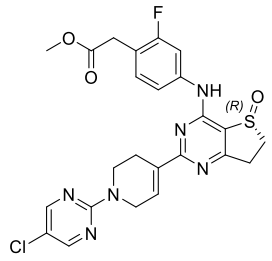
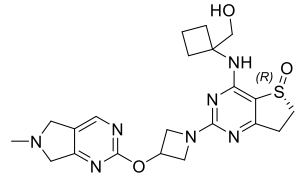
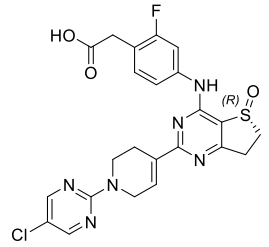
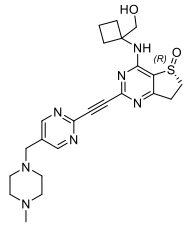
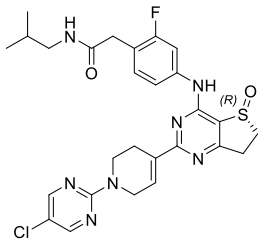
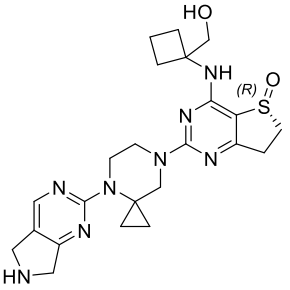
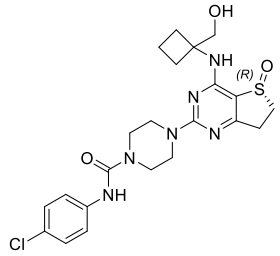
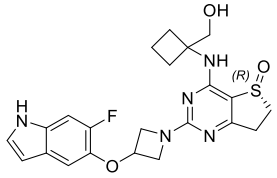
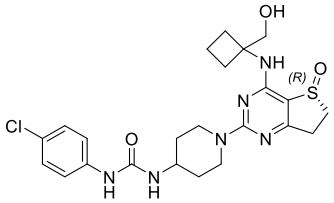
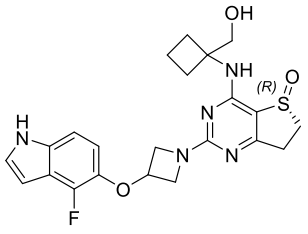
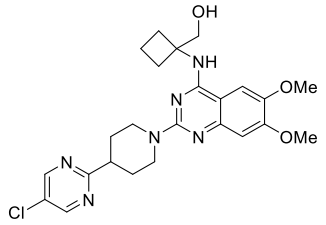
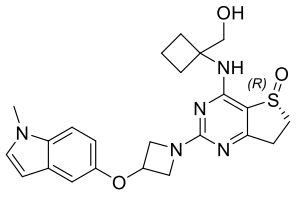
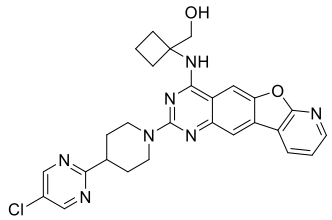
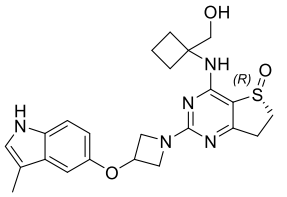
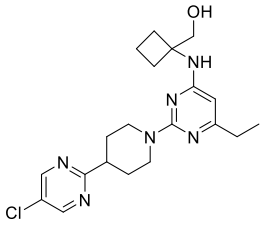
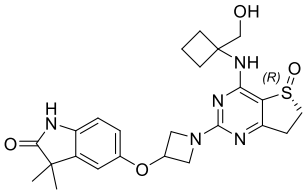
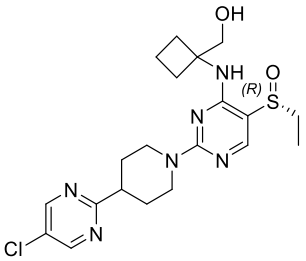
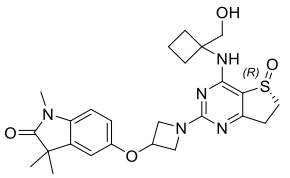
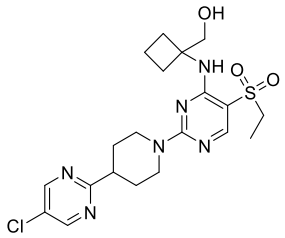
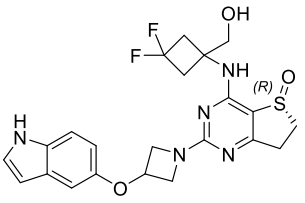
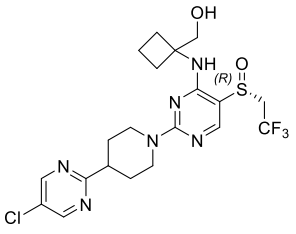
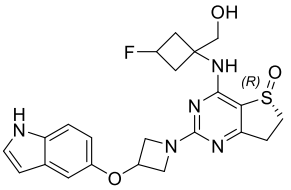
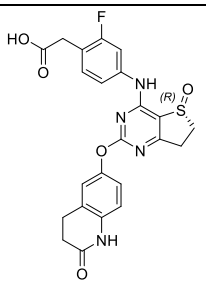
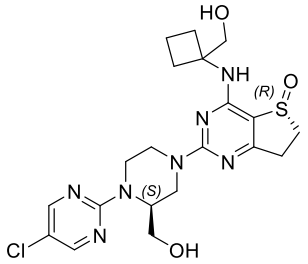
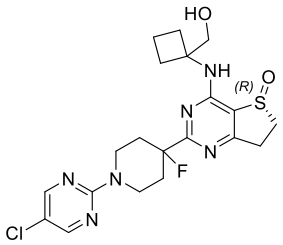
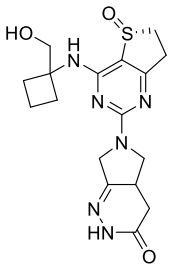
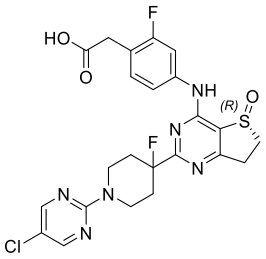
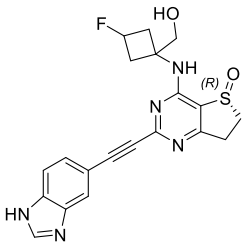
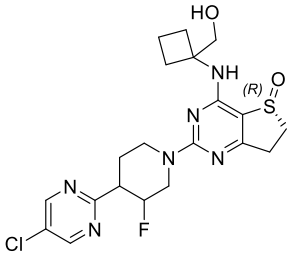
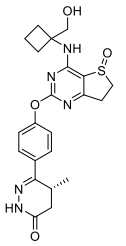
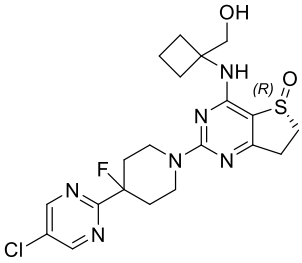
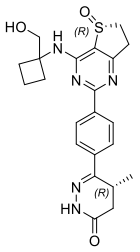
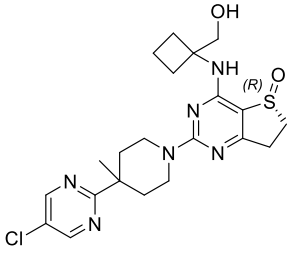
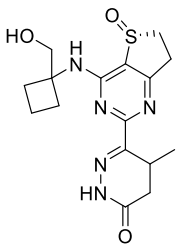
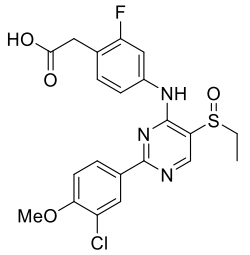
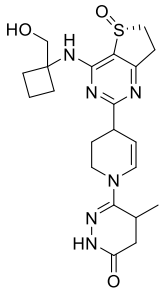
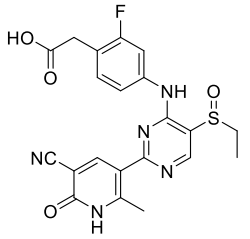
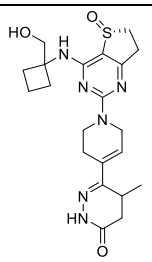
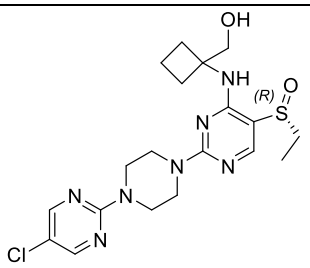
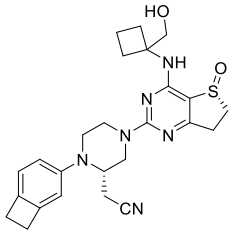
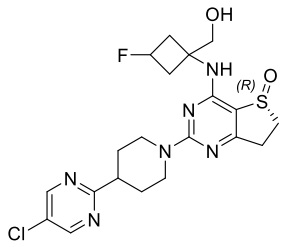
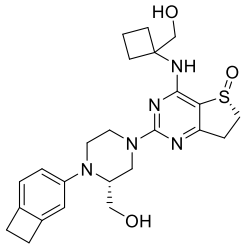
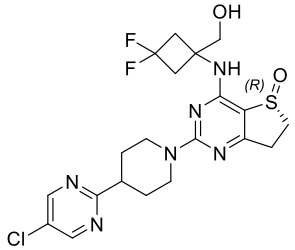
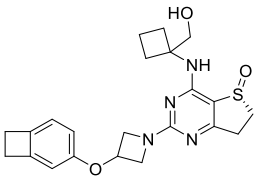
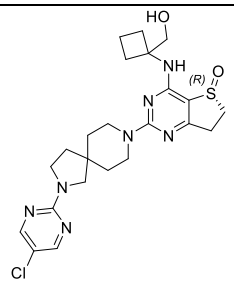
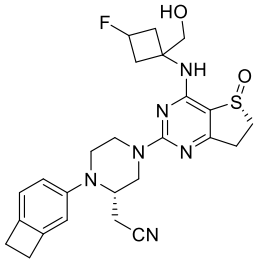
116		433	
117		434	
118		435	
119		436	
120		437-rac	
121		437-peak 1	

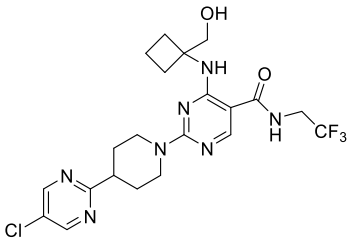
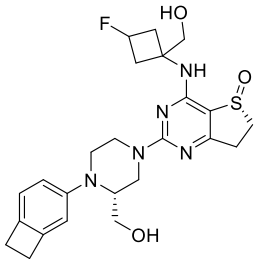
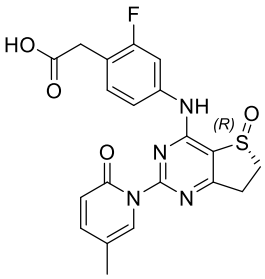
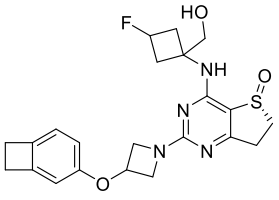
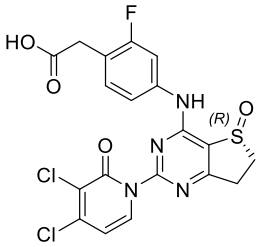
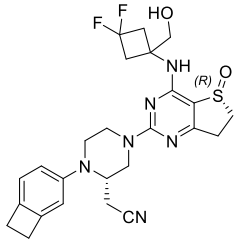
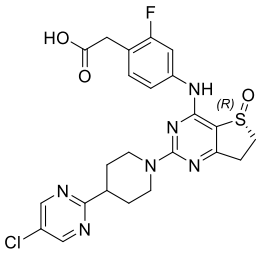
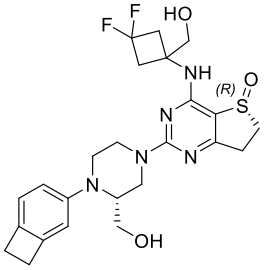
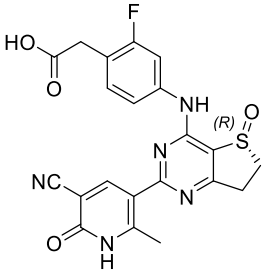
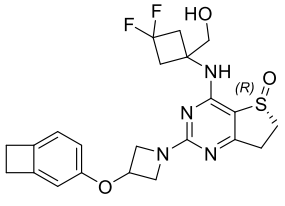
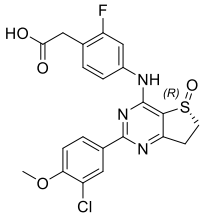
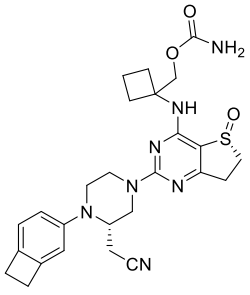
No.	Chemical Structure	No.	Chemical Structure
122		437-peak 2	
123		440	
124		445	
125		446	
126		449	
127		450	

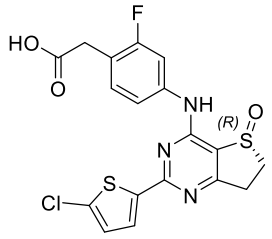
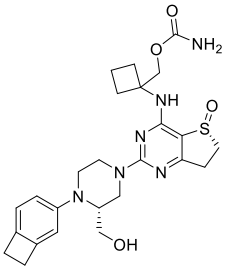
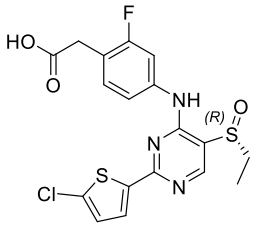
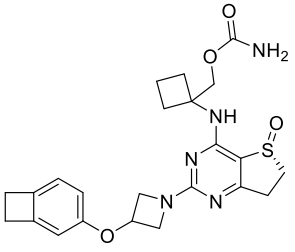
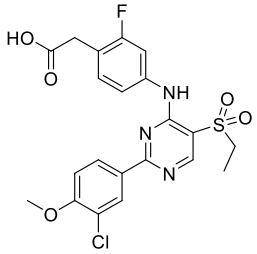
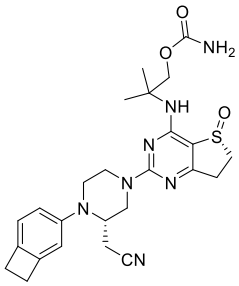
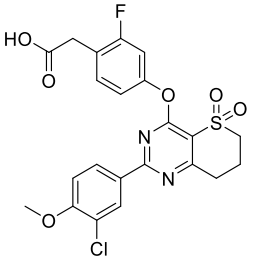
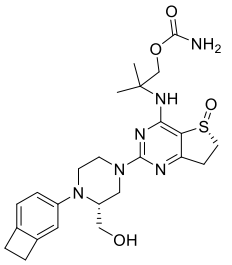
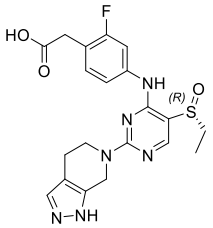
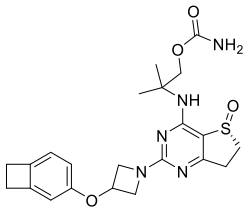
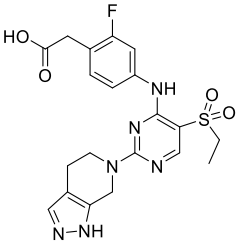
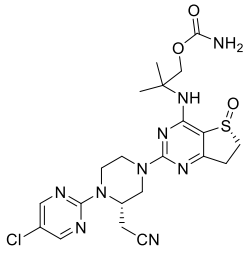
No.	Chemical Structure	No.	Chemical Structure
128		453	
129		454	
130		455	
131		456	
132		458	
133		459	

No.	Chemical Structure	No.	Chemical Structure
134		460	
135		461	
136		462	
137		463	
138		464	
139		465	

No.	Chemical Structure	No.	Chemical Structure
140		466	
141		467	
142		470	
143		472-rac	
145		473	
146		476	

No.	Chemical Structure	No.	Chemical Structure
147rac		477	
148rac		478	
149		479	
150		480	
151		481	
152		482	

No.	Chemical Structure	No.	Chemical Structure
153		483	
154		484	
155		485	
156		486	
157		487	
158		488	

No.	Chemical Structure	No.	Chemical Structure
159		489	
160		490	
161		491	
162		492	
163		493	
164		494	

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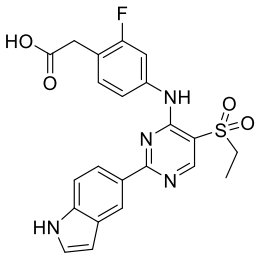
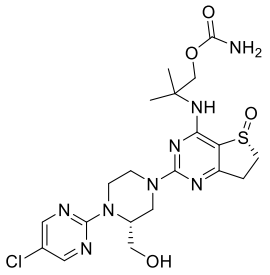
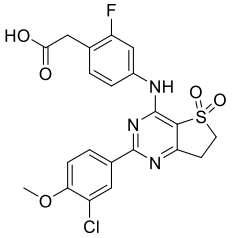
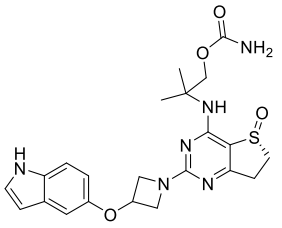
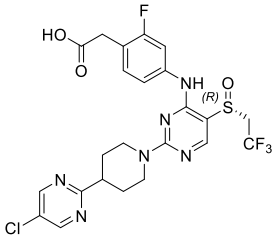
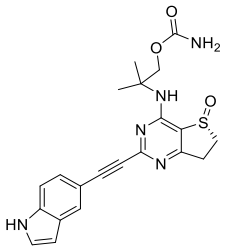
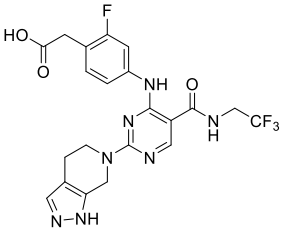
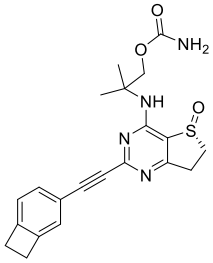
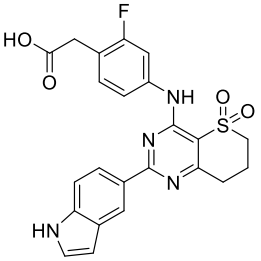
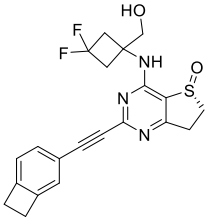
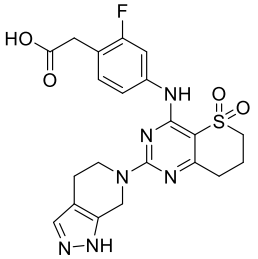
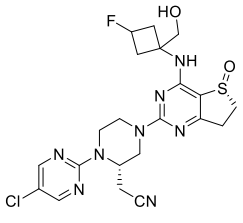
165		495	
166		496	
167		497	
168		498	
169		499	
170		520	

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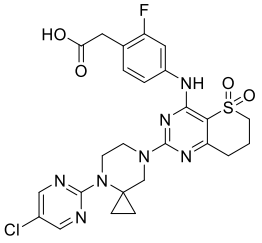
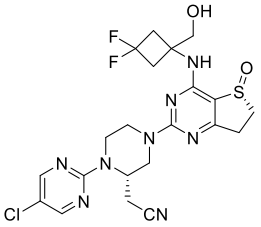
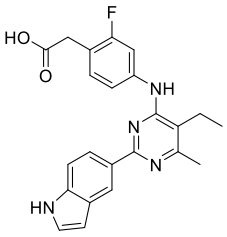
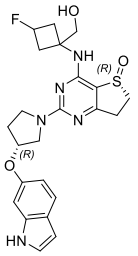
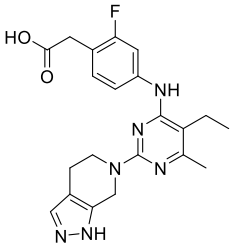
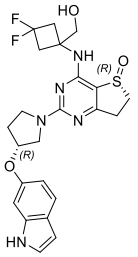
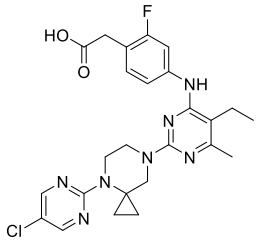
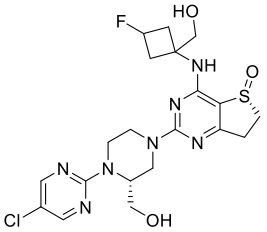
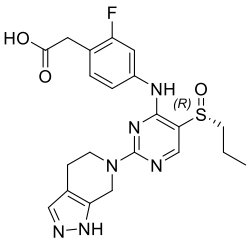
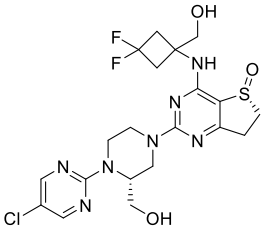
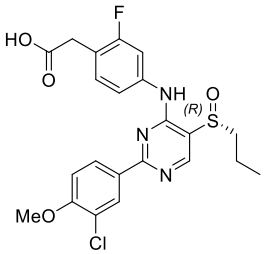
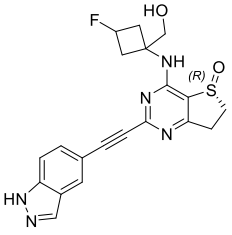
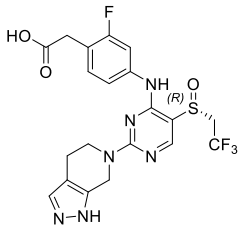
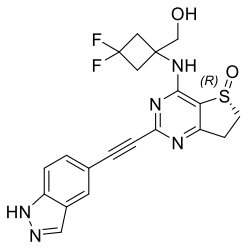
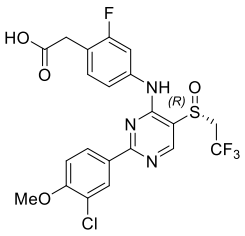
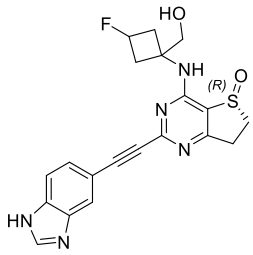
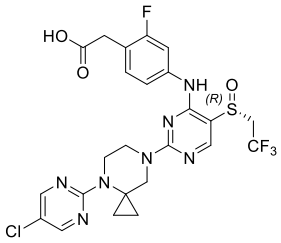
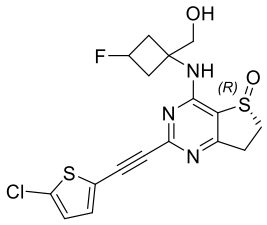
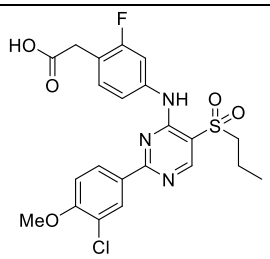
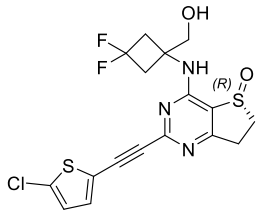
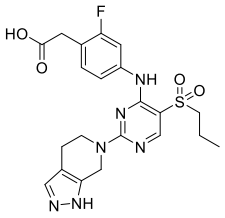
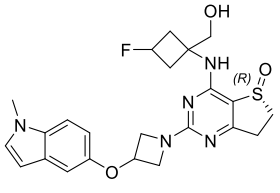
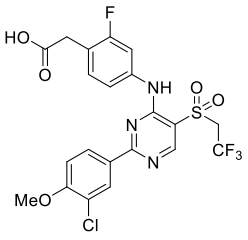
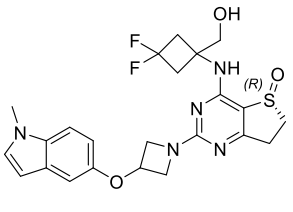
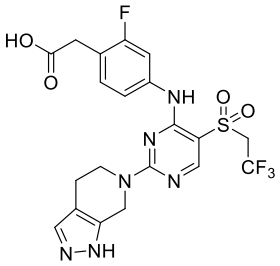
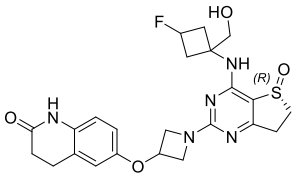
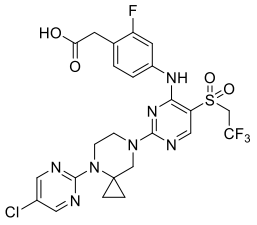
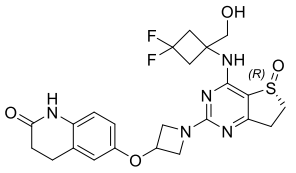
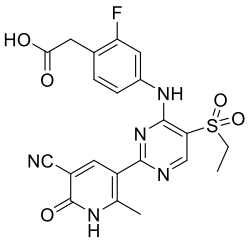
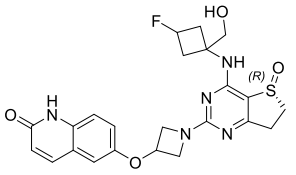
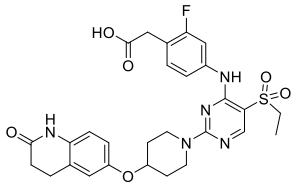
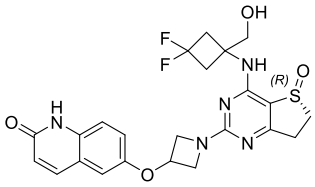
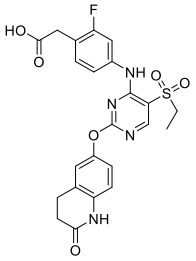
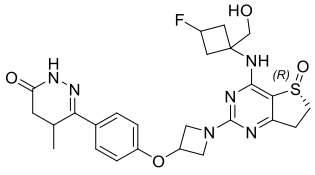
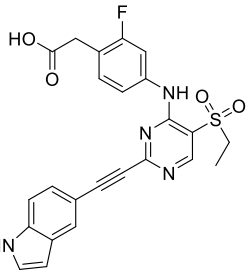
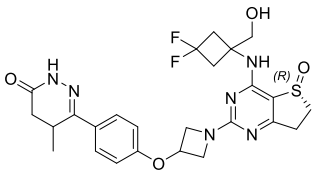
171		521	
172		522	
173		523	
174		524	
175		525	
176		526	

No.	Chemical Structure	No.	Chemical Structure
177		527	
178		528	
179		529	
180		530	
181		531	
182		532	

No.	Chemical Structure	No.	Chemical Structure
183		533	
184		534	
185		535	
186		536	
187		537	
188		538-rac	

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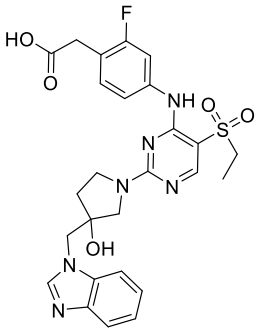
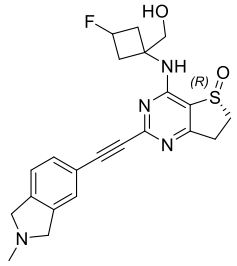
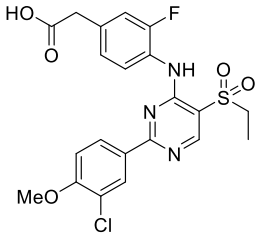
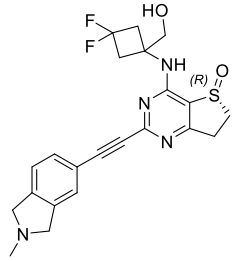
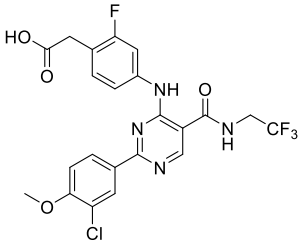
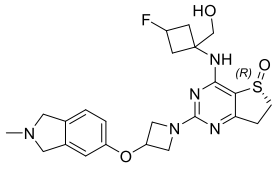
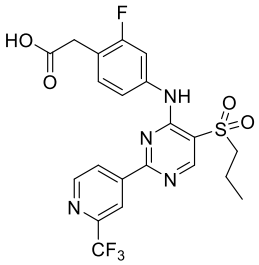
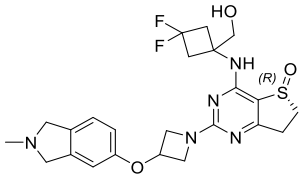
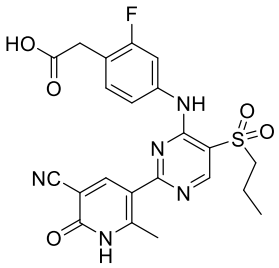
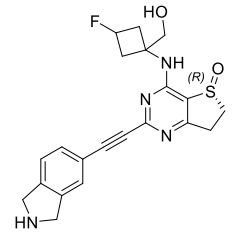
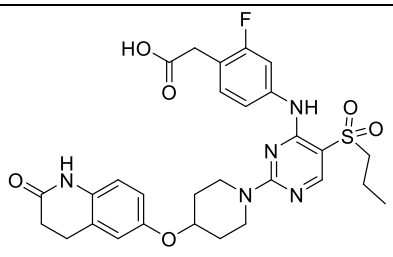
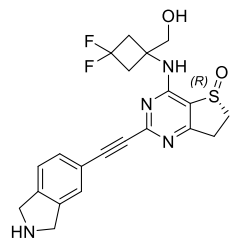
189		539	
190		540	
191		541	
192		542	
193		543	
194		544	

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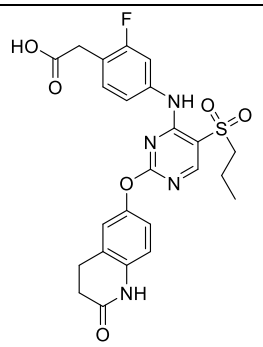
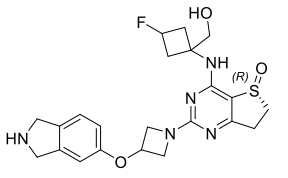
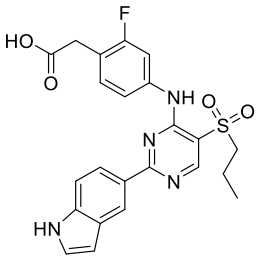
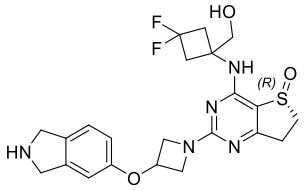
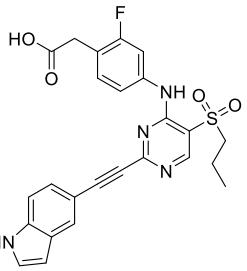
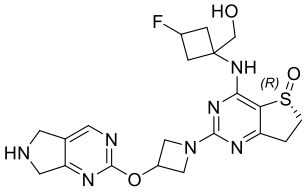
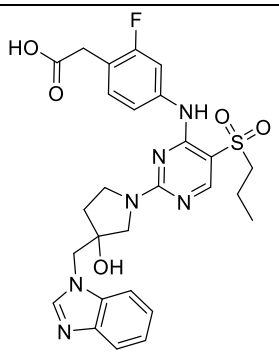
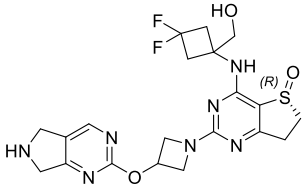
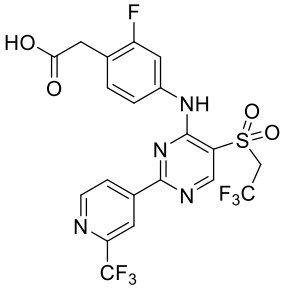
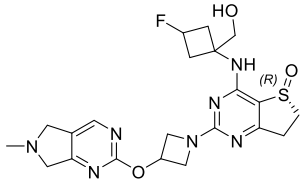
195		545	
196		546	
197		547	
198		548	
199		549	

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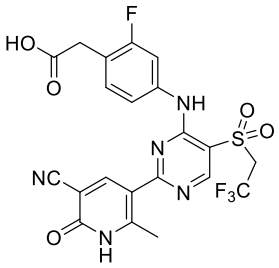
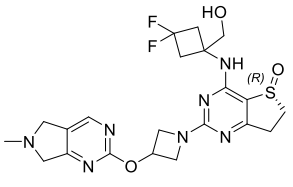
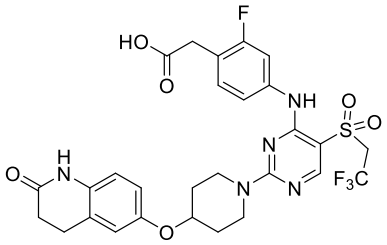
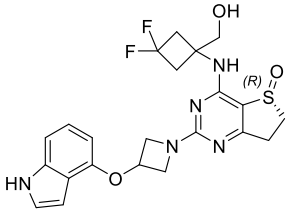
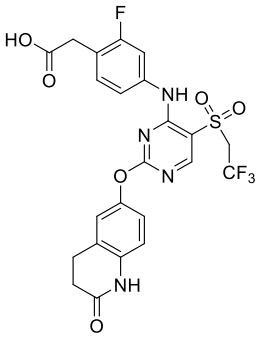
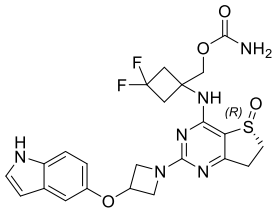
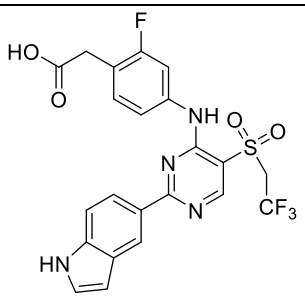
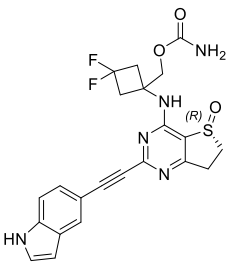
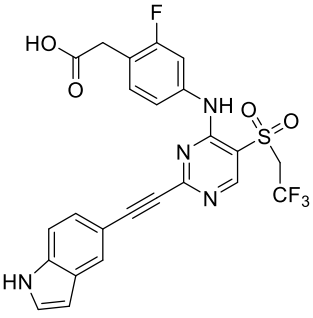
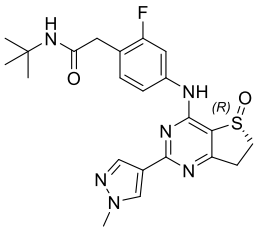
200		550	
201		578	
202		579	
203		584	
204		590	

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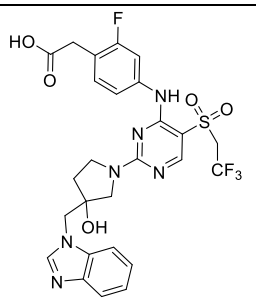
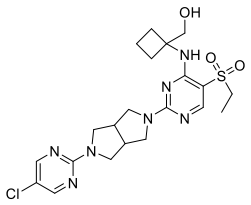
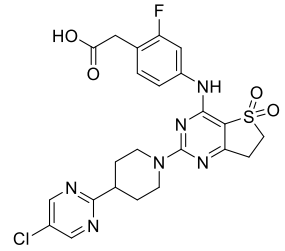
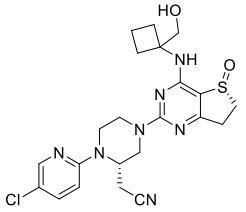
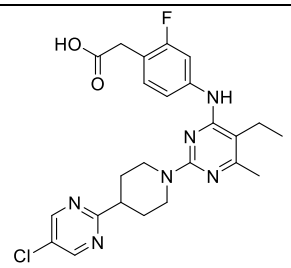
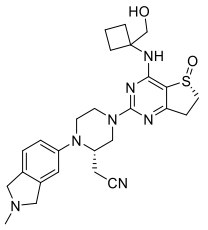
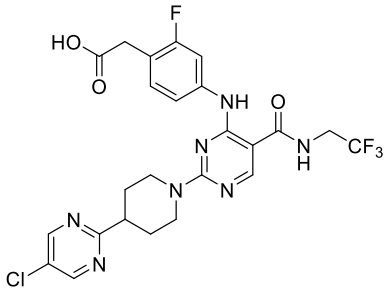
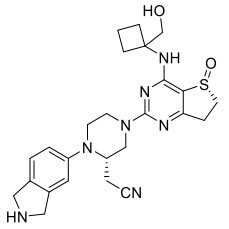
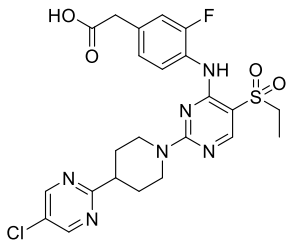
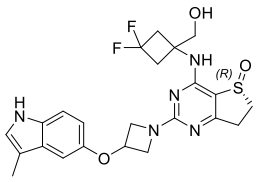
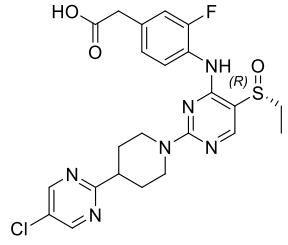
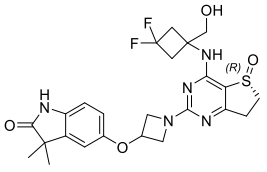
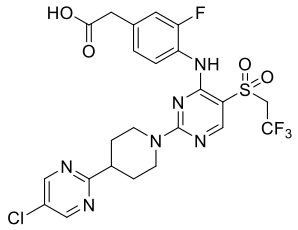
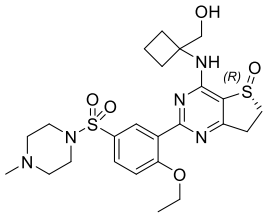
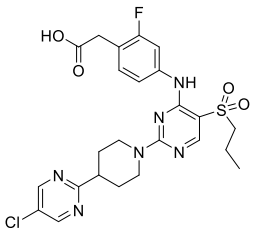
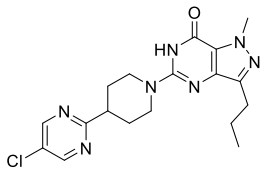
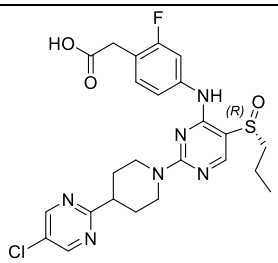
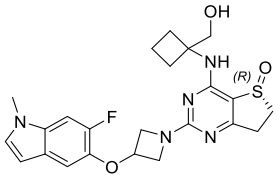
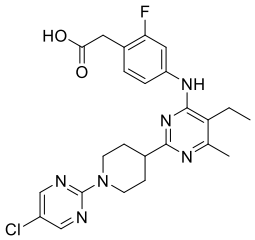
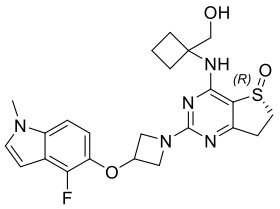
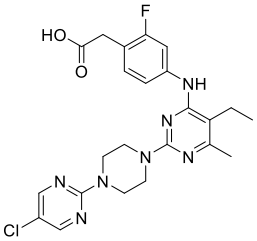
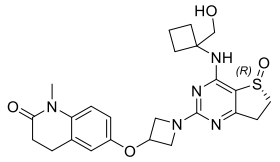
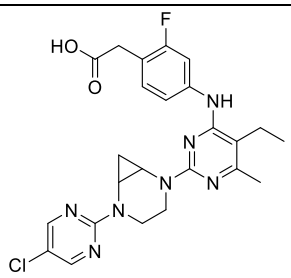
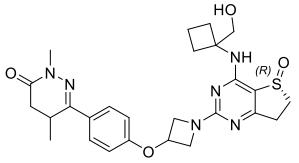
205		596	
206		597	
207		598	
208		599	
209		605	
210		606	

No.	Chemical Structure	No.	Chemical Structure
211		607	
212		608	
213		609	
214		610	
215		611	
216		612-rac	

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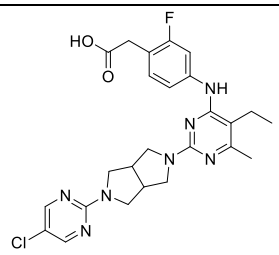
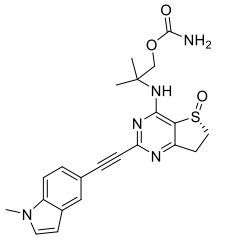
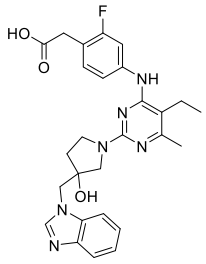
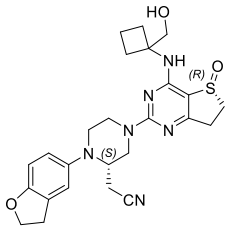
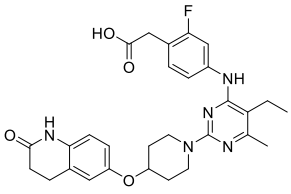
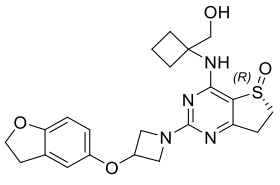
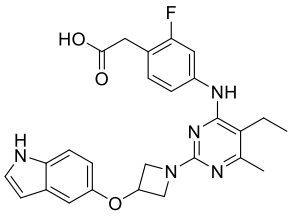
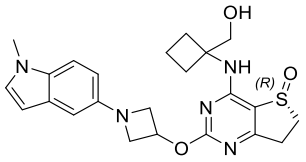
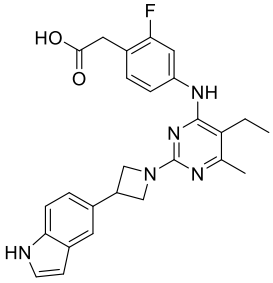
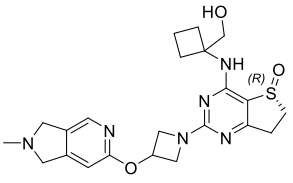
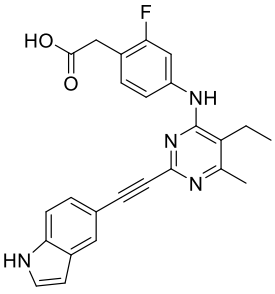
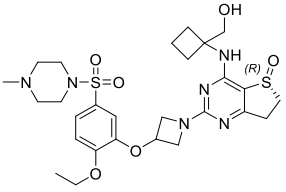
217		613	
218		614	
219		615	
220		616	
221		617	
222		618	

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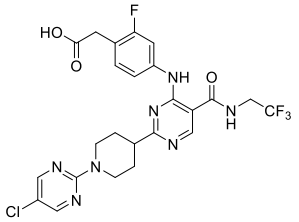
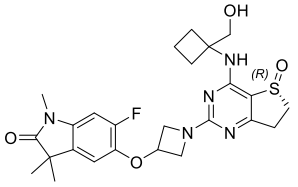
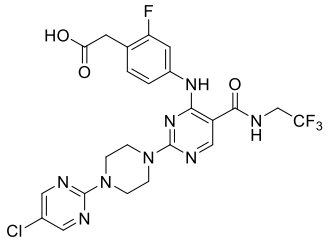
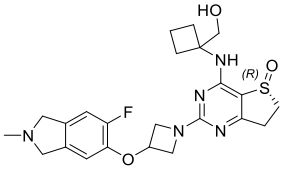
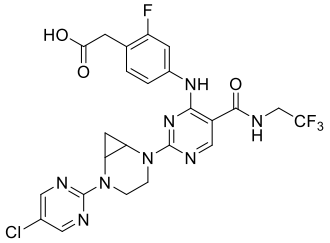
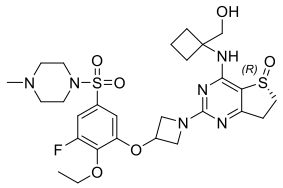
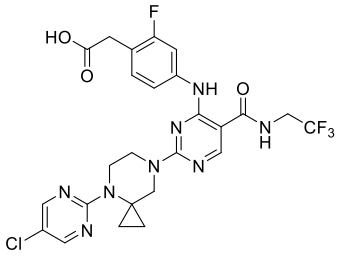
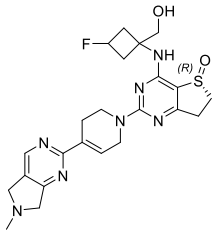
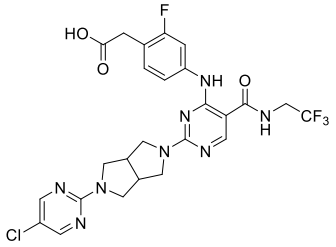
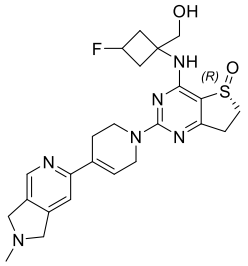
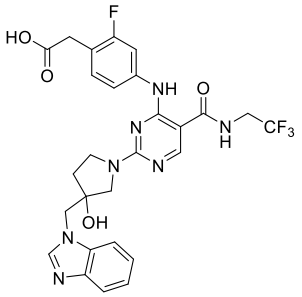
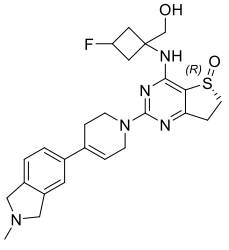
223		619	
224		620	
225		621	
226		622	
227		623	
228		624	

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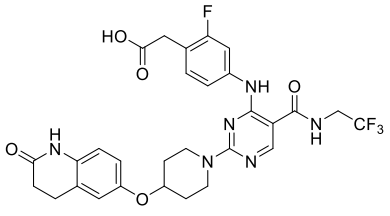
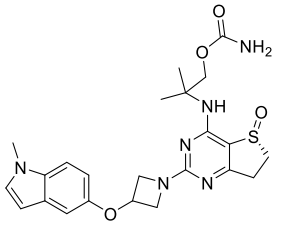
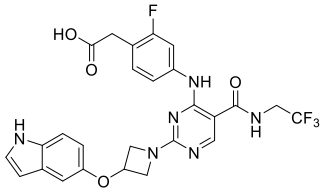
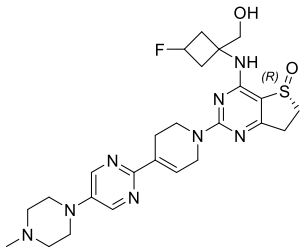
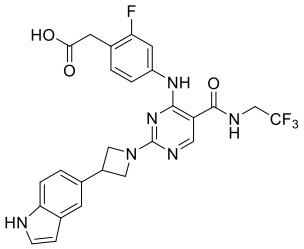
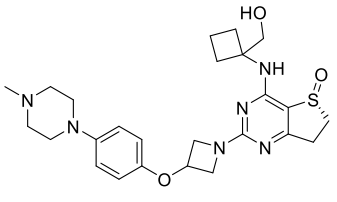
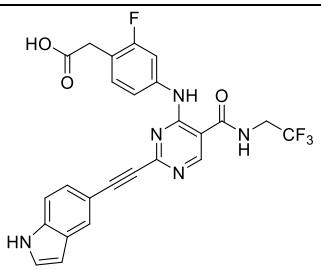
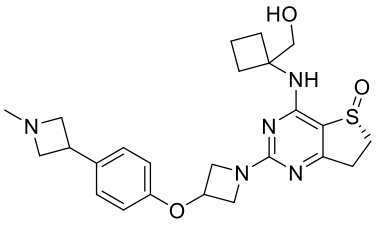
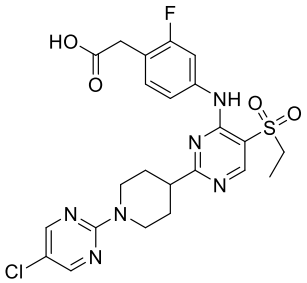
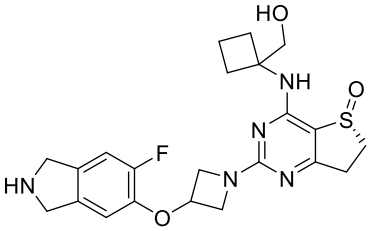
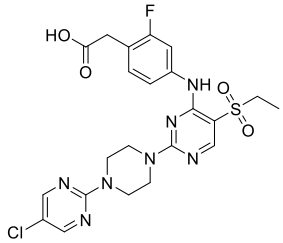
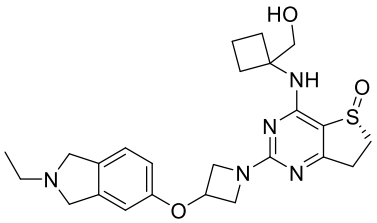
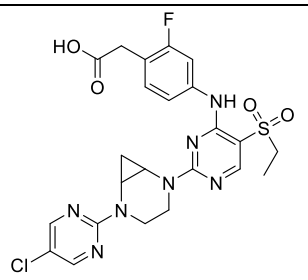
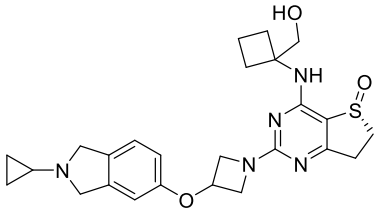
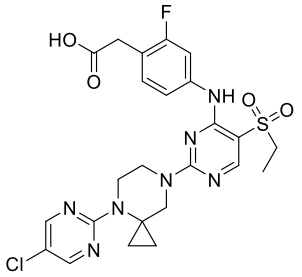
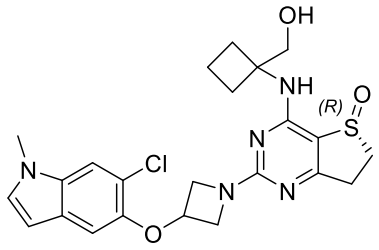
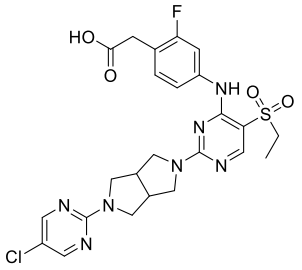
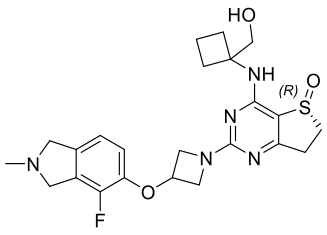
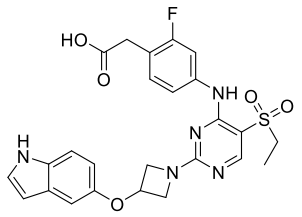
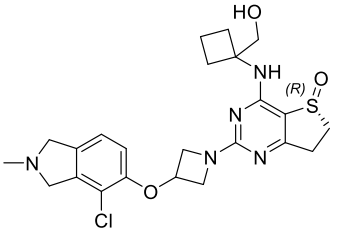
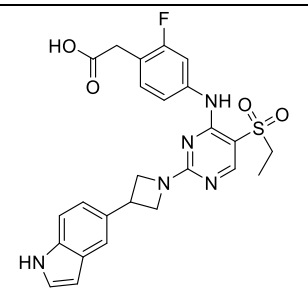
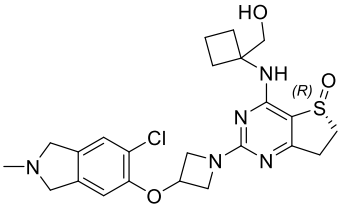
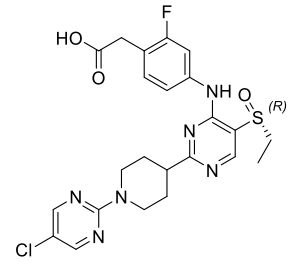
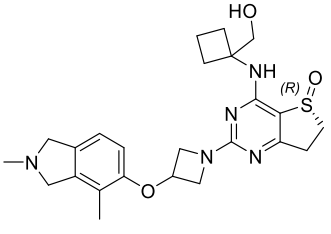
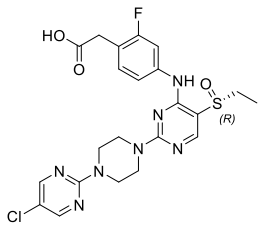
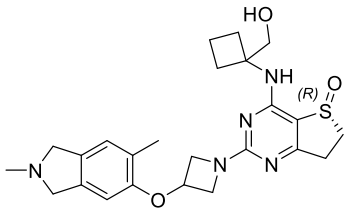
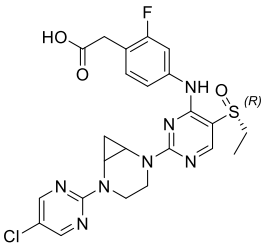
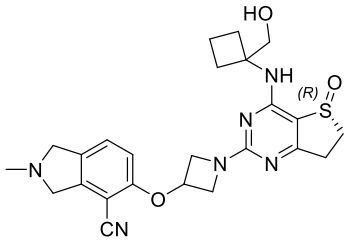
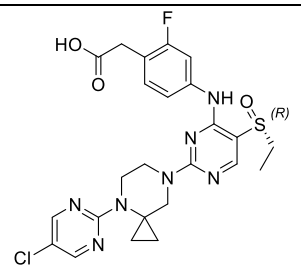
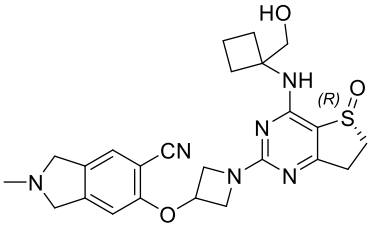
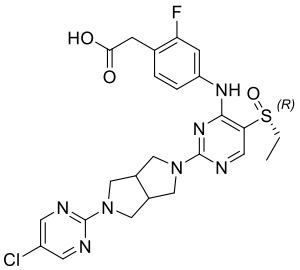
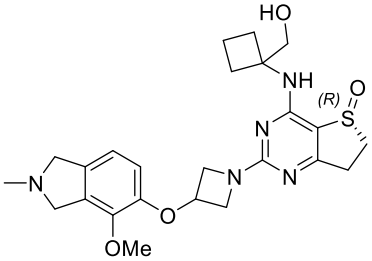
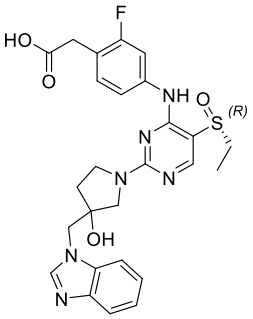
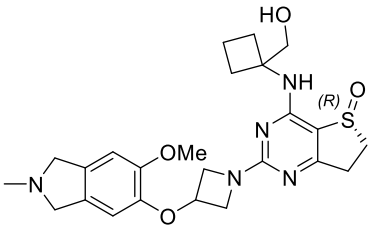
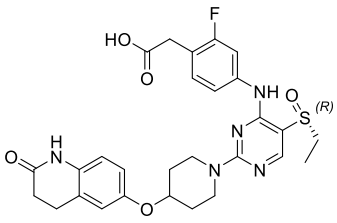
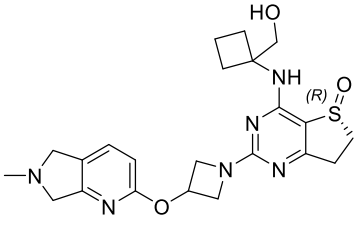
229		625	
230		626	
231		627	
232		628	
233		629	
234		630	

No.	Chemical Structure	No.	Chemical Structure
235		631	
236		632	
237		633	
238		634	
239		635	
240		636	

No.	Chemical Structure	No.	Chemical Structure
241		637	
242		638	
243		639	
244		640	
245		641	
246		642	

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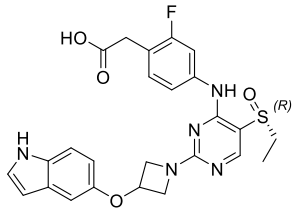
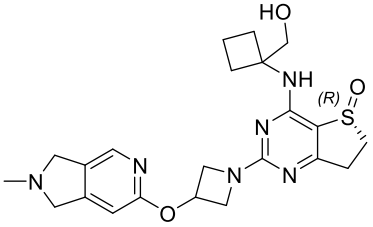
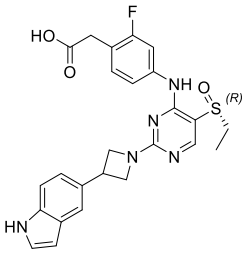
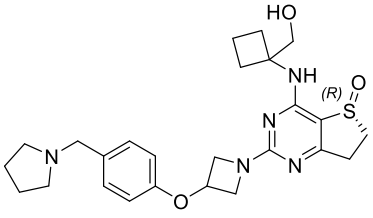
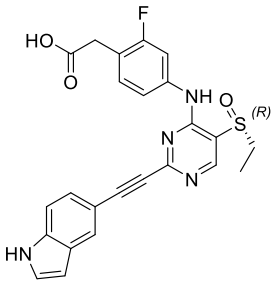
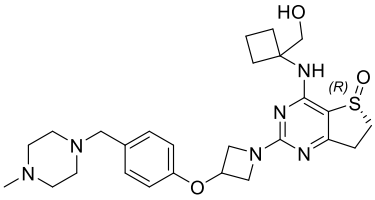
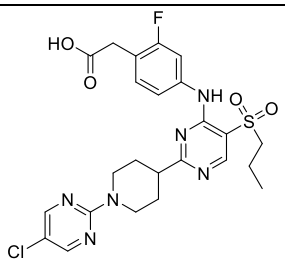
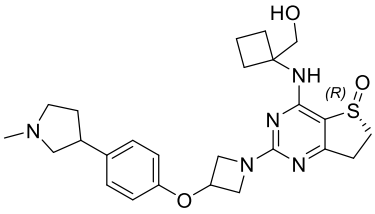
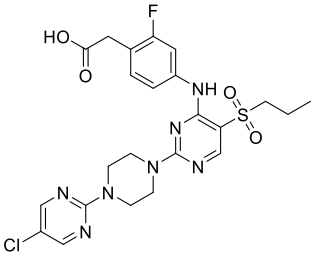
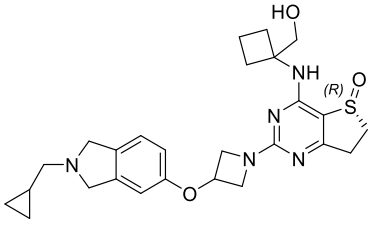
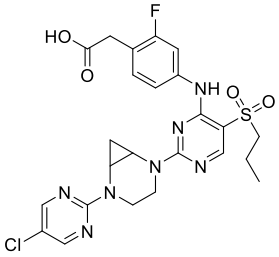
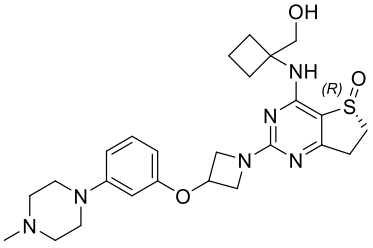
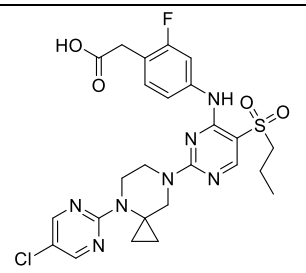
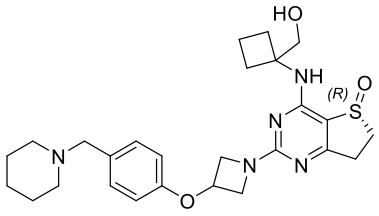
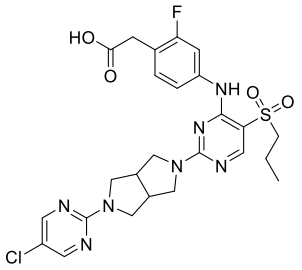
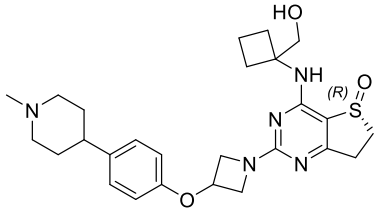
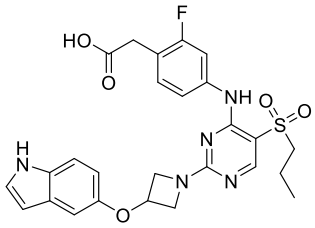
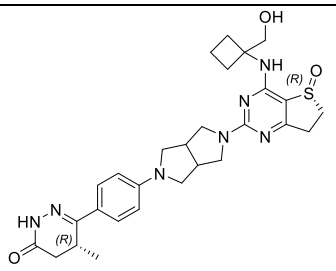
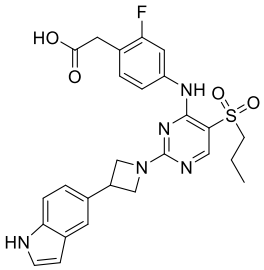
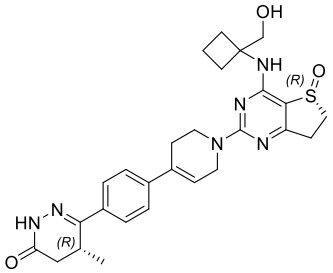
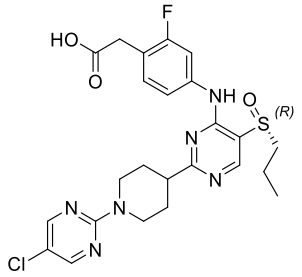
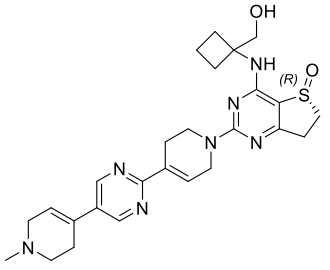
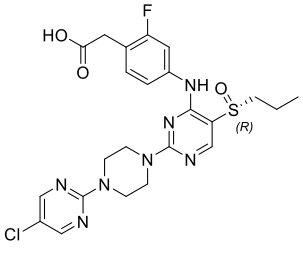
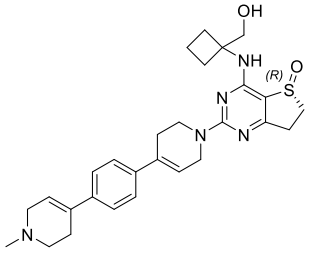
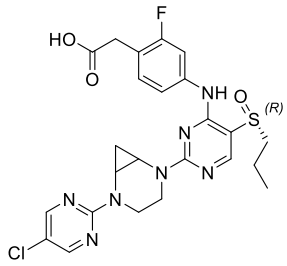
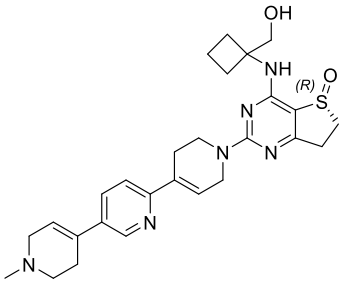
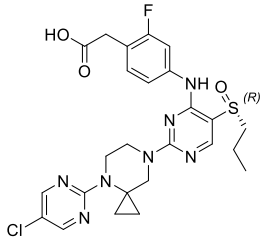
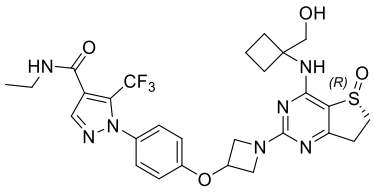
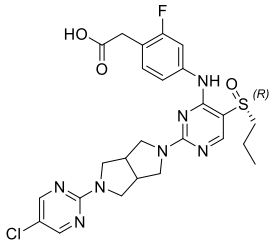
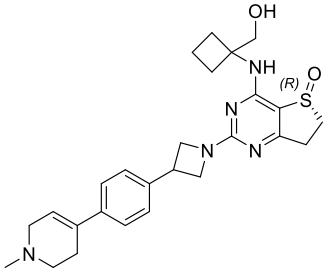
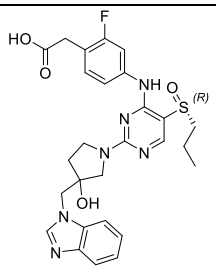
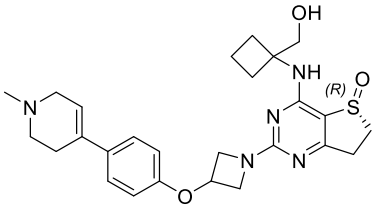
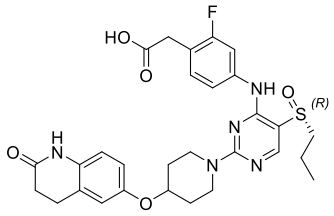
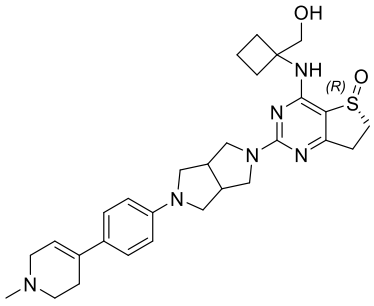
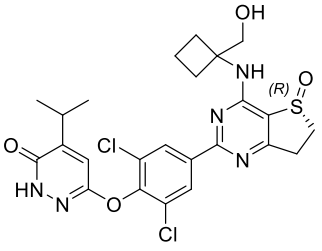
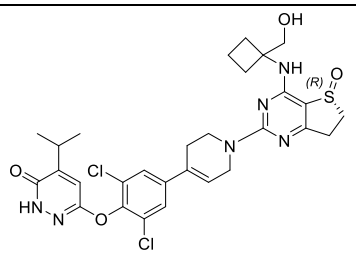
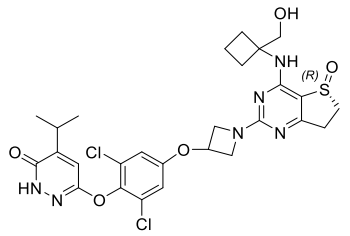
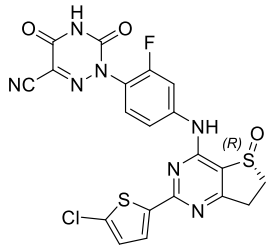
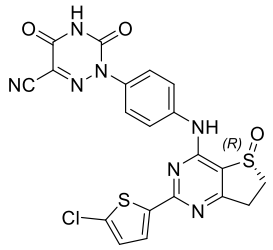
247		643	
248		644	
249		645	
250		646	
251		647	
252		648	

No.	Chemical Structure	No.	Chemical Structure
253		649	
254		650	
255		651	
256		652	
257		653	
258		654	

No.	Chemical Structure	No.	Chemical Structure
259		655	
260		656	
261		657	
262		658	
263		659	
		660	

No.	Chemical Structure	No.	Chemical Structure
		661	
		662	
		663	
		664	

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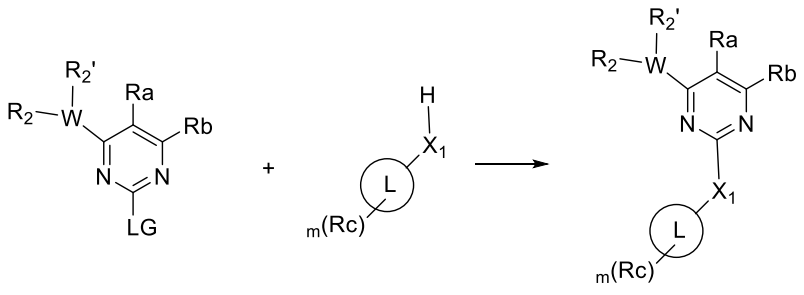
13. A preparation method for the compound or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof according to any one of claims 1-12, wherein the preparation method comprises reacting a compound of formula A1 with a compound of formula B1 to obtain the compound of formula H:



A1 B1 H

and optionally, derivatizing the compound of formula G into the stereoisomer, the tautomer,

the isotopically labeled compound, the solvate, the polymorph, the metabolite, the pharmaceutically acceptable salt, or the prodrug thereof;

wherein LG is a leaving group, such as Cl, Br, or I;

X_1, L, W, R_a, R_b, R_c, R_2, $R_{2'}$, and m are each independently defined as described in any one of claims 1-11.

14. A pharmaceutical composition, comprising a therapeutically effective amount of at least one of the compound (for example, any one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof according to any on of claims 1-12.

15. A method for preventing or treating a disease, comprising administering to a patient in need at least one of the compound (for example, any one of the compounds represented by formulas I to IX), or the racemate, the stereoisomer, the tautomer, the isotopically labeled compound, the solvate, the polymorph, the pharmaceutically acceptable salt, or the prodrug compound thereof according to any one of claims 1-12;

wherein the disease may be a PDE4B-mediated disease, or a disease mediated at least in part by PDE4;

preferably, the disease includes, but is not limited to, inflammatory diseases of the respiratory tract, inflammatory bowel diseases, arthritic diseases, dermatological inflammatory diseases, ocular inflammatory diseases, peripheral or central nervous system diseases, degenerative diseases of the central nervous system, Alzheimer's disease (AD), non-alcoholic steatohepatitis (NASH), idiopathic pulmonary fibrosis (IPF) or pulmonary hypertension associated therewith, chronic obstructive pulmonary disease (COPD) or pulmonary hypertension associated therewith, hepatic fibrosis (HF), renal fibrosis, benign prostatic hyperplasia (BPH), gastroesophageal reflux disease, obstructive sleep apnea, coronary artery disease, or cancer;

preferably, the cancer includes, but is not limited to: gastric cancer, bladder cancer, leukemia, bone cancer, brain cancer, breast cancer, central nervous system cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, gallbladder cancer, gastrointestinal cancer, external genitalia cancer, genitourinary cancer, head cancer, kidney cancer, laryngeal cancer, liver cancer, lung cancer, muscular tissue cancer, neck cancer, oral or nasal mucosa cancer, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, splenic cancer, small intestine cancer, colorectal cancer, testicular cancer, and/or thyroid cancer;

preferably, lesions of the disease may include the respiratory system, the digestive system, the excretory system, and/or the reproductive system, e.g., the liver, the kidney, and/or the prostate. For this purpose, the medicament may be a targeted drug for the respiratory system, the digestive system, the excretory system, and/or the reproductive system, such as a liver-targeted drug, a kidney-targeted drug, and/or a prostate-targeted drug.