

**DIHYDROPYRIMIDINE-2,4(1H,3H)-DIONE-CONTAINING POLYCYCLIC
DERIVATIVES AND PHARMACEUTICAL COMPOSITION THEREOF,
PREPARATION METHOD THEREOF AND USE THEREOF**

5 TECHNICAL FIELD

The present disclosure relates to medicinal chemistry, in particular, dihydropyrimidine-2,4(1H,3H)-dione-containing polycyclic compounds, or pharmaceutically acceptable salts thereof, and compositions thereof which are effective to reduce or modulate widely interspaced zinc finger motifs (WIZ) protein expression levels and/or induce fetal hemoglobin (HbF) expression, and also relates to methods of their preparation and their use in treatment of subjects in need.

BACKGROUND

Sickle cell disease (SCD) is caused by the formation of a pathological sickle hemoglobin tetramer consisting of two α -globin chains and two abnormal β -globin chains (HbS), in which the glutamic acid residue at position 6 is replaced by valine owing to a single base change, from adenine to thymine, in the β -globin gene (HBB) (Rees DC et al., *Lancet* 2010, 376: 2018-2031). Polymerization of deoxygenated HbS causes abnormally shaped red blood cells, painful vaso-occlusive episodes, hemolytic anemia, end-organ damage, and early death resulting in high economic burden and poor quality of life (Martin B et al., Societal Burden of Sick cell Disease in the United Kingdom, 17th Annual Academy for Sick cell and Thalassemia (ASCAT) Conference, 2022, October 20-22).

Increasing HbF levels in adult red blood cells provides considerable amelioration of the symptoms in SCD patients and a subset of β -Thalassemia patients (Grevet JD et al., *Science* 2018, 361: 285-290). Hydroxyurea, an approved drug, is considered to achieve its benefit by enhancing the production of HbF. However, there is still limited data to support the long-term benefits of hydroxyurea for all SCD patients, particularly in preventing chronic complications of SCD (Nevitt SJ et al., *Cochrane Database Syst Rev* 2017, 4: CD002202). As such, SCD patients are in urgent need of new treatment options to improve the quality of life and to reduce long-term health care costs (Piel FB et al., *N Engl J Med* 2017, 376: 1561-1573).

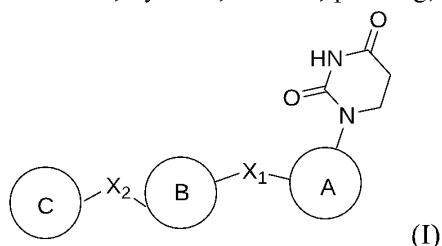
The G9a methyltransferase is known to regulate HbF production by repressing the transcription of fetal γ -globin genes (Krivega, et al. *Blood*, 2015). WIZ was reported to retain histone H3 lysine 9 methyltransferases G9a and GLP on chromatin to direct the

deposition of H3K9me1 and H3K9me2, resulting in gene repression (Bian C *et al.*, *Elife* 2015, 4: e05606) thereby, potentially contributing to the silencing of γ -globin genes. WIZ is a known neosubstrate of several CRBN-based molecular glue degraders including immunomodulatory (IMiD) drugs and CC-122 (Yu HH *et al.*, *bioRxiv* 2019 (doi: <https://doi.org/10.1101/595389>); Hagner PR *et al.*, *Blood*. 2015, 126: 779-789). Recruitment of WIZ to the Cul4/DDB1/RBX1/CRBN E3 ligase complex by these compounds results in ubiquitination and subsequent proteasomal degradation of WIZ via a mechanism commonly shared among IMiD substrates (Sievers, Q. L. *et al.* *Science* 2018, 362, eaat0572). Therefore, WIZ degradation by molecular glues represents a promising therapeutic strategy in SCD and β -thalassemia by restoring γ -globin synthesis and HbF production.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a new class of compounds which can reduce/modulate WIZ protein expression levels.

In the first aspect, it provides a compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,



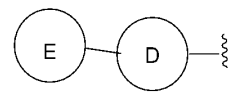
wherein:

X_1 and X_2 are each independently selected from the group consisting of a bond, $-(CH_2)_n-$, $-CH(R^1)(CH_2)_n-$, $-C(O)-$, and $-S(O)_2-$;

Ring A is independently selected from the group consisting of C_6 - C_{10} aryl, monocyclic 5- or 6-membered heteroaryl, bicyclic 9- or 10-membered heteroaryl, and tricyclic 12-, 13- or 14-membered heteroaryl, wherein the heteroaryl has 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N, wherein the aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^2 ;

Ring B is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C_6 - C_{10} aryl, 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N;

wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^3 ;



Ring C is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_6 - C_{10} aryl-fused C_5 - C_{10} cycloalkyl, C_6 - C_{10} heteroaryl-fused C_5 - C_{10} cycloalkyl, C_6 - C_{10} aryl-fused 5 to 10-membered heterocyclyl, and C_6 - C_{10} heteroaryl-fused 5 to 10-membered heterocyclyl; wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are independently selected from the group consisting of O, S, and N; wherein the C_6 - C_{10} aryl-fused C_5 - C_{10} cycloalkyl, C_6 - C_{10} heteroaryl-fused C_5 - C_{10} cycloalkyl, C_6 - C_{10} aryl-fused 5 to 10-membered heterocyclyl, and C_6 - C_{10} heteroaryl-fused 5 to 10-membered heterocyclyl are optionally substituted with 1 to 6 identical or different substituents R^4 ;

Ring D is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_6 - C_{10} aryl, and 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^5 ;

Ring E is independently selected from the group consisting of absence, C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_6 - C_{10} aryl, and 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^6 ;

wherein n is 0, 1, 2 or 3,

the H in $-(CH_2)_n-$ can be optionally substituted with deuterium, C_1 - C_6 alkyl, and halogen;

each R^1 is independently selected from the group consisting of H, deuterium, C_1 - C_6 alkyl, and halogen;

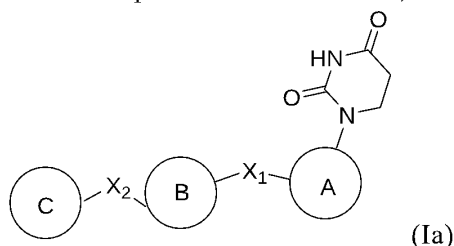
each R^2 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

each R^3 and R^5 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyloxy, C_2 - C_6 alkynyloxy, C_2 - C_6 alkanoyl, C_2 - C_6 alkylester, C_1 - C_6 thioalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, hydroxy C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, and 3 to

8-membered heterocyclyl, wherein the cycloalkyl, and heterocyclyl are optionally substituted with halogen, CN and -OMe;

each R^4 and R^6 is independently selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, -CN, -OH, C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, nitro, amino, mercapto, -COOH, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_2 - C_6 alkenyloxy, C_2 - C_6 alkynyloxy, C_2 - C_6 alkanoyl, C_2 - C_6 alkylester, C_1 - C_6 thioalkyl, hydroxy C_1 - C_6 alkyl, amino C_1 - C_6 alkyl, (mono- and di- C_1 - C_6 alkylamino) C_0 - C_4 alkyl, $-C_0$ - C_4 alkyl(C_3 - C_7 cycloalkyl), $-O$ - C_0 - C_4 alkyl(C_3 - C_7 cycloalkyl), $-C_0$ - C_4 alkyl-(phenyl), $-C_0$ - C_4 alkylOC(O)OC C_1 - C_6 alkyl, $-C_0$ - C_4 alkylOC(O)C C_1 - C_6 alkyl, $-C_0$ - C_4 alkylC(O)OC C_1 - C_6 alkyl, C_0 - C_4 alkyl-(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and C_0 - C_4 alkyl-(5- or 6- membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, $-C(O)OR^7$, $-C_0$ - C_4 alkylNR $^7R^8$, $-C(O)NR^7R^8$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-OC(O)R^7$, and $-C(NR^7)NR^7R^8$, wherein R^7 and R^8 are independently chosen from hydrogen, C_1 - C_6 alkyl, $-C_0$ - C_4 alkyl(C_3 - C_7 cycloalkyl), and $-O$ - C_0 - C_4 alkyl(C_3 - C_7 cycloalkyl).

In another preferred embodiment, the compound has the structure of formula (Ia):



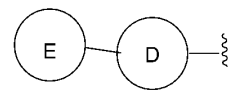
wherein:

X_1 and X_2 are each independently selected from the group consisting of a bond, $-(CH_2)_n$ -, $-CH(R^1)(CH_2)_n$ -, $-C(O)$ -, and $-S(O)_2$ -;

Ring A is independently selected from the group consisting of C_6 - C_{10} aryl, monocyclic 5- or 6-membered heteroaryl, bicyclic 9- or 10-membered heteroaryl, and tricyclic 12-, 13- or 14-membered heteroaryl, wherein the heteroaryl has 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N, wherein the aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^2 ;

Ring B is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C_6 - C_{10} aryl, 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N;

wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^3 ;



Ring C is independently selected from the group consisting of C_6 - C_{10} aryl-fused C_5 - C_7 cycloalkyl, C_6 - C_{10} heteroaryl-fused C_5 - C_7 cycloalkyl, C_6 - C_{10} aryl-fused 5 to 7-membered heterocyclyl, and C_6 - C_{10} heteroaryl-fused 5 to 7-membered heterocyclyl; wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are independently selected from the group consisting of O, S, and N; wherein the C_6 - C_{10} aryl-fused C_5 - C_7 cycloalkyl, C_6 - C_{10} heteroaryl-fused C_5 - C_7 cycloalkyl, C_6 - C_{10} aryl-fused 5 to 7-membered heterocyclyl, and C_6 - C_{10} heteroaryl-fused 5 to 7-membered heterocyclyl are optionally substituted with 1 to 6 identical or different substituents R^4 ;

Ring D is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_6 - C_{10} aryl, and 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^5 ;

Ring E is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_6 - C_{10} aryl, and 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^6 ;

wherein n is 0, 1, 2 or 3,

the H in $-(CH_2)_n-$ can be optionally substituted with deuterium, C_1 - C_6 alkyl, and halogen;

each R^1 is independently selected from the group consisting of H, deuterium, C_1 - C_6 alkyl, and halogen;

each R^2 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

each R^3 and R^5 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyloxy, C_2 - C_6 alkynyloxy, C_2 - C_6 alkanoyl, C_2 - C_6 alkylester, C_1 - C_6 thioalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, hydroxy C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, and 3 to

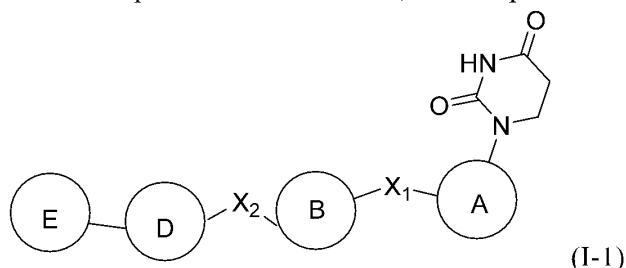
8-membered heterocyclyl, wherein the cycloalkyl, and heterocyclyl are optionally substituted with halogen, CN and -OMe;

each R^4 and R^6 is independently selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, -CN, and -OH.

5 In another preferred embodiment, X_1 is $-CH_2-$ or $-CD_2-$.

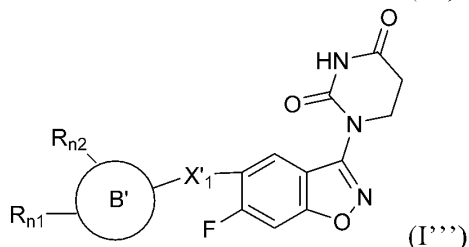
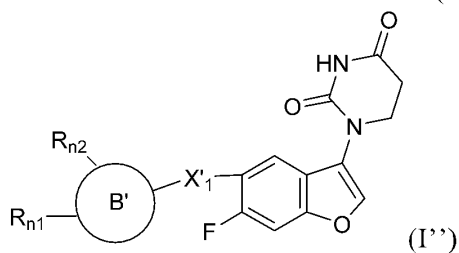
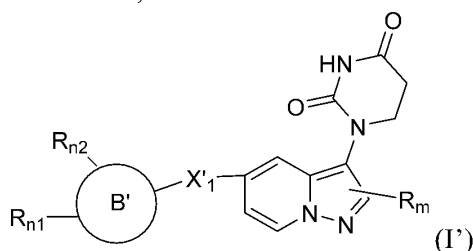
In another preferred embodiment, X_2 is $-CH_2-$ or $-CD_2-$.

In another preferred embodiment, the compound has the structure of formula (I-1):



wherein X_1 , X_2 , Ring A, Ring B, Ring D and Ring E are defined as above.

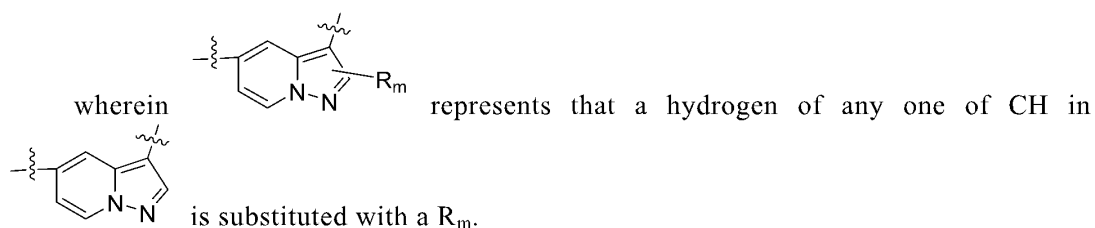
10 In another preferred embodiment, it provides a compound of formula (I'), (I'') or (I'''), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,



15

wherein

R_m is independently selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, -CN, and -OH;



X'₁ is -(CH₂)_m-, -CH(R_{n1}')-(CH₂)_m-, -C(O)-, or -S(O)₂-;

Ring B' is independently selected from the group consisting of C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C₆-C₁₀ aryl, 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N;

R_{n1}, R_{n2} and R_{n1}' are each independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C₆-C₁₀ aryl, and 5 to 10-membered heteroaryl; wherein the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl;

the H in -(CH₂)_m- can be optionally substituted with deuterium, C₁-C₆ alkyl, and halogen;

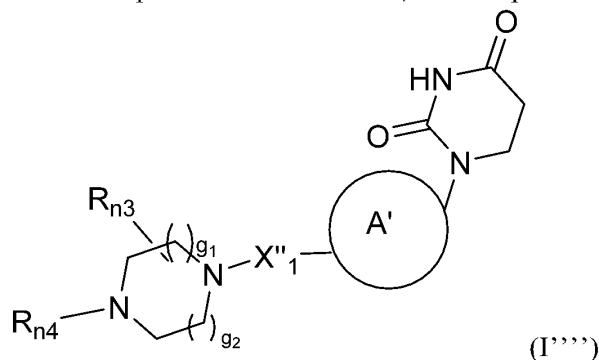
m is 0, 1, 2, or 3.

In another preferred embodiment, X'₁ is -(CH₂)- or -(CD₂)-.

In another preferred embodiment, Ring B' is selected from the group consisting of 4 to 6 membered monocyclic heterocyclyl, preferably Ring B' is selected from the group consisting of piperazinyl and piperidinyl.

In another preferred embodiment, R_{n1}, R_{n2} and R_{n1}' are each independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In another preferred embodiment, the compound has the structure of formula (I''')



wherein, Ring A' is independently selected from the group consisting of C₆-C₁₀ aryl, monocyclic 5- or 6-membered heteroaryl, bicyclic 9- or 10-membered heteroaryl, and tricyclic 12-, 13- or 14-membered heteroaryl, wherein the heteroaryl has 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N, wherein the aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^{2'};

each R^{2'} is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

X''₁ is -(CH₂)_m-, -CH(R_{n3})(CH₂)_m-, -C(O)-, or -S(O)₂-;

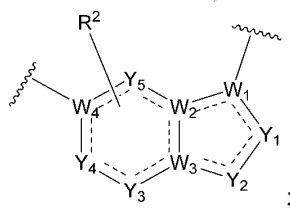
R_{n3} is independently selected from the group consisting of C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C₆-C₁₀ aryl, and 5 to 10-membered heteroaryl; wherein the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, and -OH;

R_{n4} is independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C₆-C₁₀ aryl, and 5 to 10-membered heteroaryl; wherein the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl;

g₁ and g₂ are each independently 0, 1 or 2.

In another preferred embodiment, Ring A' has the same definition as Ring A.

In another preferred embodiment, wherein Ring A is 9-membered heteroaryl, and



preferably, Ring A is

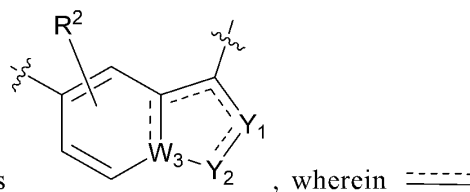
wherein ----- is a single bond or a double bond;

R² is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

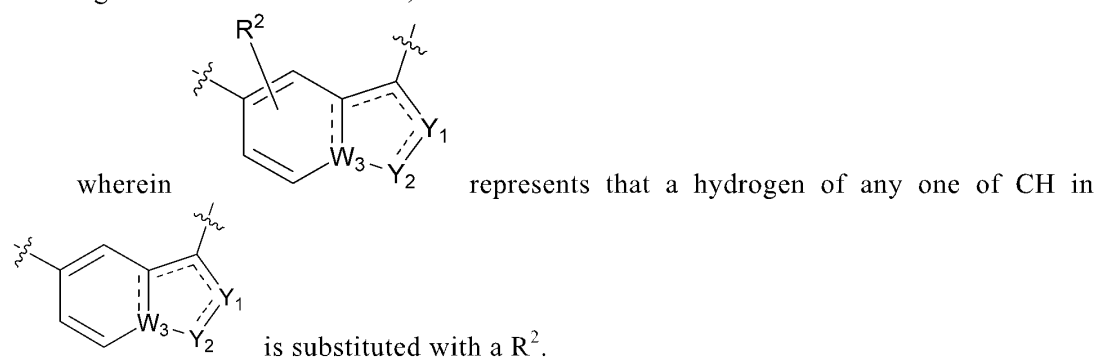
Y₁, Y₂, Y₃, Y₄ and Y₅ are each independently selected from the group consisting of C, CH, N, O, S and CO;

W₁, W₂, W₃ and W₄ are each independently selected from the group consisting of C,

and N.



In another preferred embodiment, Ring A is
is a single bond or a double bond;

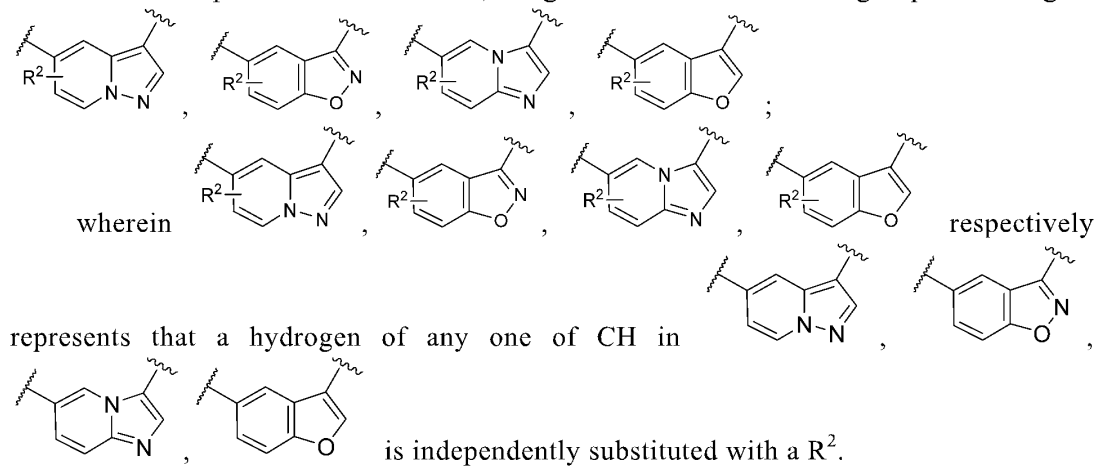


R^2 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

Y_1 and Y_2 are each independently selected from the group consisting of C, CH, N, O, S and CO;

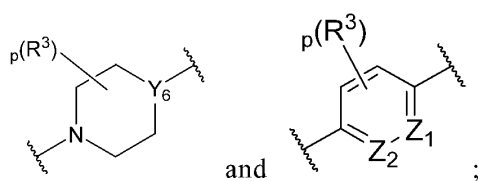
10 W_3 is independently selected from the group consisting of C, and N.

In another preferred embodiment, Ring A is selected from the group consisting of



wherein each R^2 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl.

In another preferred embodiment, Ring B is selected from the group consisting of



Y₆ is independently selected from the group consisting of CH and N;

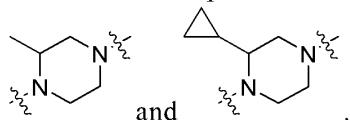
Z₁ and Z₂ are each independently selected from the group consisting of CH and N;

each R³ is independently selected from the group consisting of hydrogen, halogen,

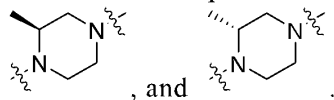
- 5 hydroxyl, nitro, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₆ alkanoyl, C₂-C₆ alkylester, C₁-C₆ thioalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, hydroxy C₁-C₆ alkyl, C₃-C₇ cycloalkyl, and 3 to 8-membered heterocyclyl, wherein the cycloalkyl, and heterocyclyl are optionally substituted with halogen, CN and -OMe;

- 10 p is 0, 1, 2, 3 or 4.

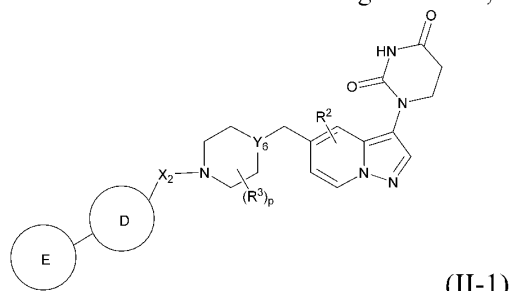
In another preferred embodiment, Ring B is selected from the group consisting of,



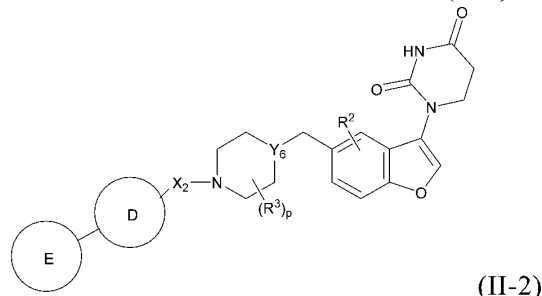
In another preferred embodiment, Ring B is selected from the group consisting of



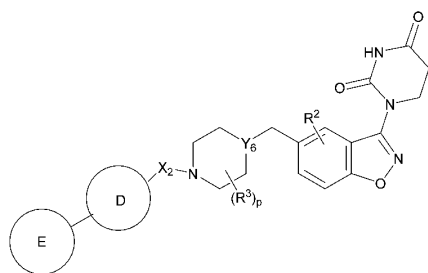
- 15 In another preferred embodiment, the compound has a structure represented by a formula selected from the following formulas,



(II-1)



(II-2)



(II-3)

wherein, each X_2 is independently selected from the group consisting of a bond, $-(CH_2)_n-$, $-CH(R^1)(CH_2)_n-$, $-C(O)-$, and $-S(O)_2-$;

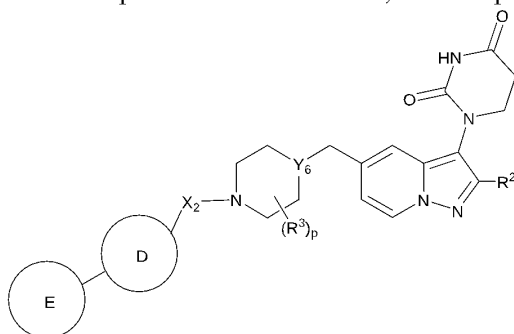
Y_6 is independently selected from the group consisting of CH and N;

5 p is 0, 1, 2, 3 or 4;

n is 0, 1, 2 or 3;

R^1 , R^2 , R^3 , Ring D and Ring E are defined as above.

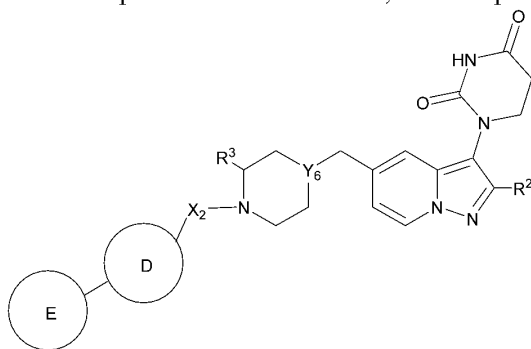
In another preferred embodiment, the compound has a structure of formula (III)



(III)

10 wherein R^2 , R^3 , X_2 , p , Y_6 , Ring D and Ring E are defined as above.

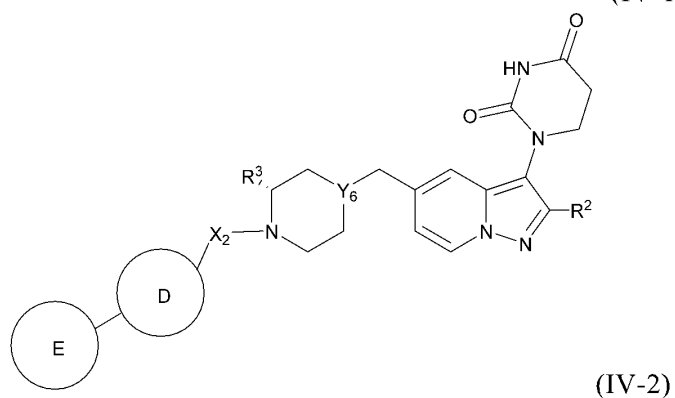
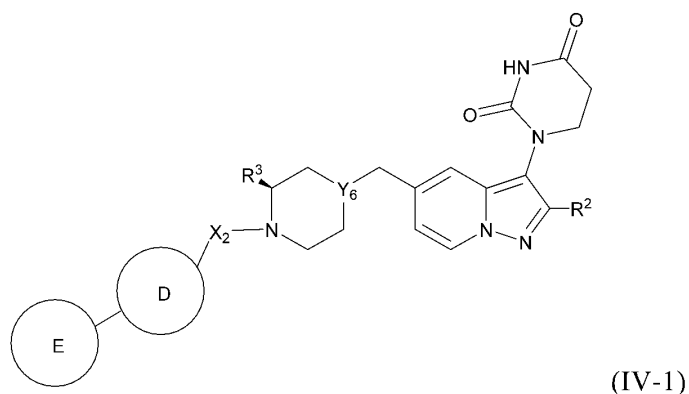
In another preferred embodiment, the compound has a structure of formula (IV)



(IV)

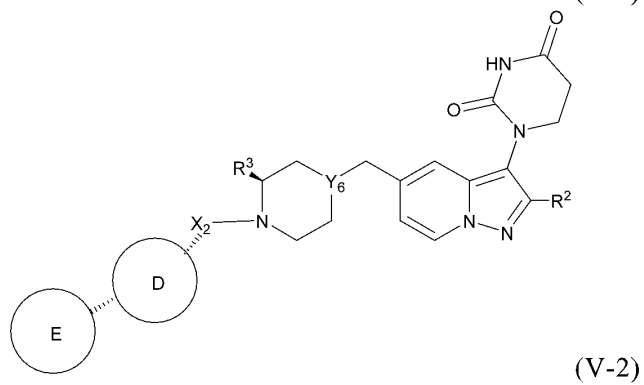
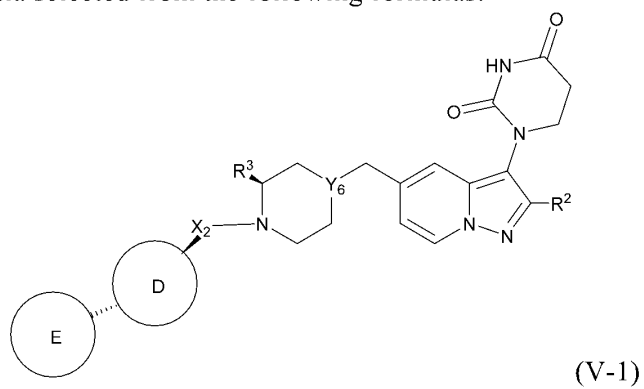
wherein R^2 , R^3 , X_2 , Y_6 , Ring D and Ring E are defined as above.

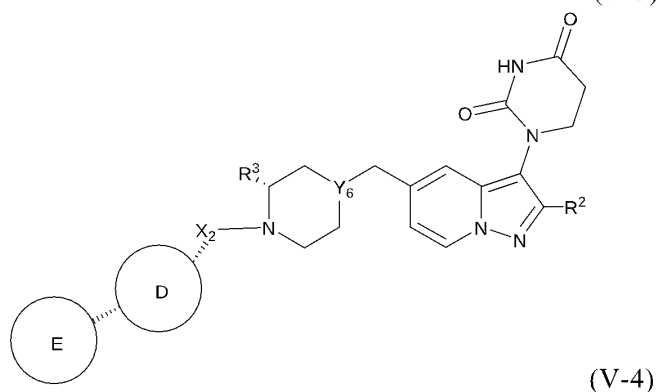
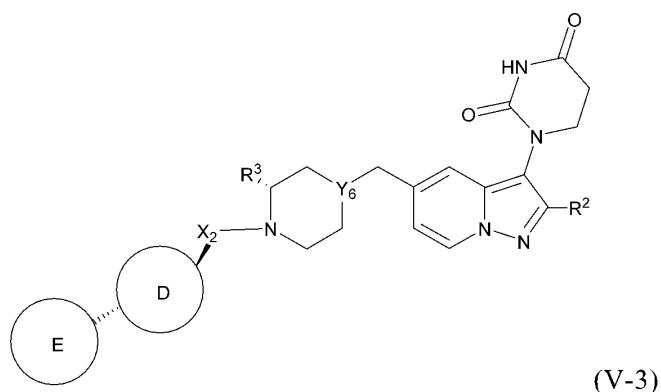
15 In another preferred embodiment, the compound has a structure represented by a formula selected from the following formulas



wherein R^2 , R^3 , X_2 , Y_6 , Ring D and Ring E are defined as above.

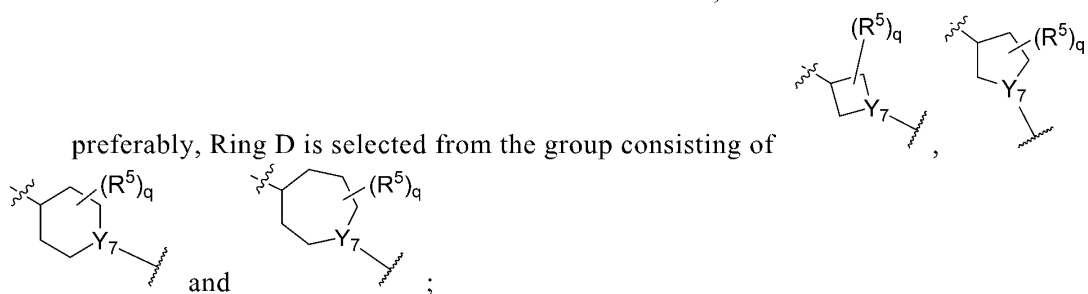
In another preferred embodiment, the compound has a structure represented by a
 5 formula selected from the following formulas:





wherein R^2 , R^3 , X_2 , Y_6 , Ring D and Ring E are defined as above.

In another preferred embodiment, Ring D is selected from the group consisting of
 5 C_3 - C_7 cycloalkyl (preferably, C_3 - C_6 cycloalkyl), 4-8-membered heterocyclyl (preferably,
 4-7-membered heterocyclyl), wherein the cycloalkyl and heterocyclyl are optionally
 substituted with 1 to 6 identical or different substituents R^5 ;

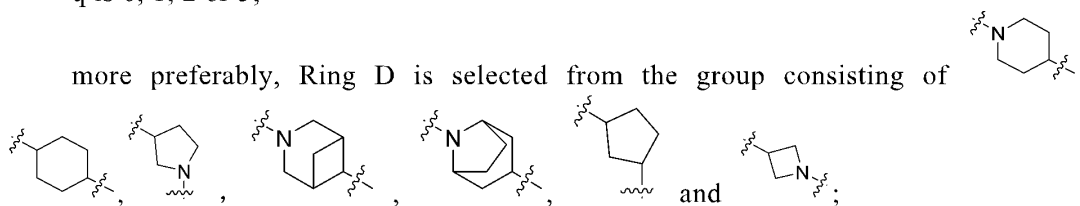


10 wherein, each R^5 is independently selected from the group consisting of hydrogen,
 halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy,
 C_2 - C_6 alkenyloxy, C_2 - C_6 alkynyloxy, C_2 - C_6 alkanoyl, C_2 - C_6 alkylester, C_1 - C_6 thioalkyl,
 C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, hydroxy C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, and 3 to
 15 substituted with halogen, CN and -OMe; or two R^5 on non-adjacent carbon atoms together
 with the non-adjacent carbon atoms to which they are attached form a bridging ring;

Y_7 is independently selected from the group consisting of CH and N;

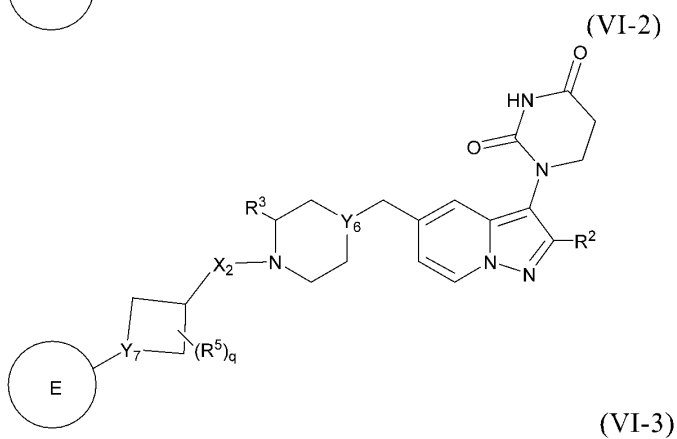
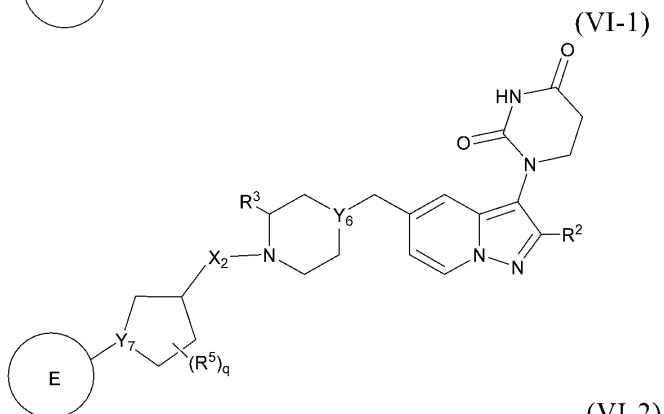
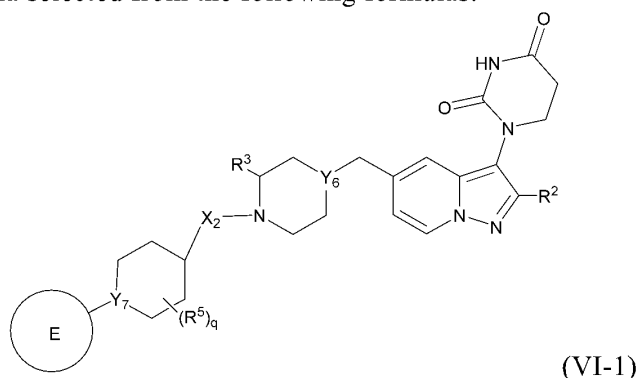
q is 0, 1, 2 or 3;

more preferably, Ring D is selected from the group consisting of

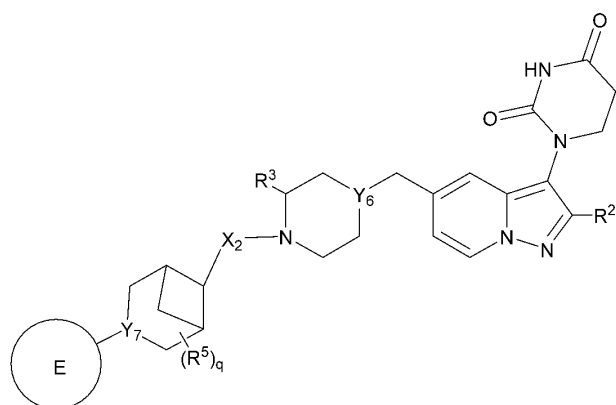


more preferably, each R^5 is independently selected from the group consisting of
 5 hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_3 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_3 haloalkyl.

In another preferred embodiment, the compound has a structure represented by a formula selected from the following formulas:

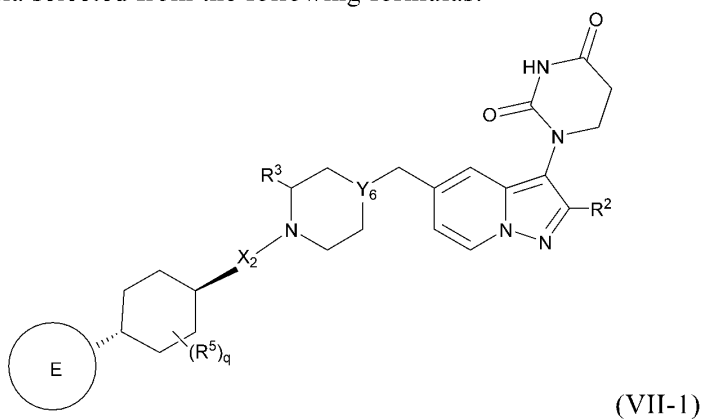


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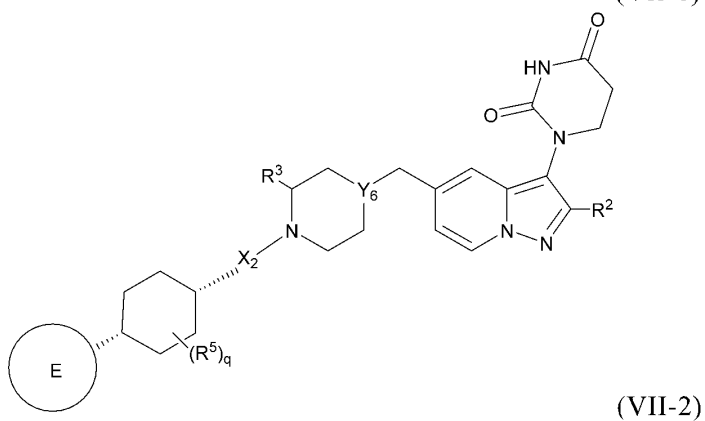


wherein R^2 , R^3 , R^5 , X_2 , q , Y_6 , Y_7 , and Ring E are defined as above.

In another preferred embodiment, the compound has a structure represented by a formula selected from the following formulas:

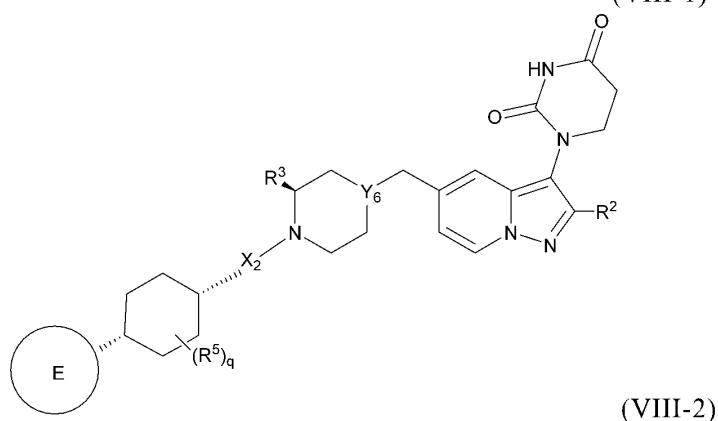
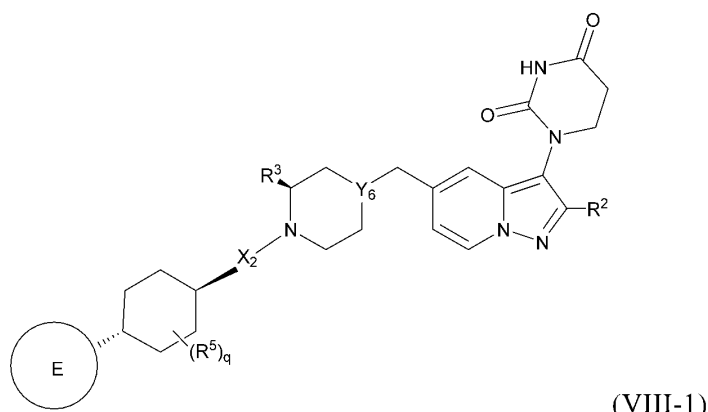


5



wherein R^2 , R^3 , R^5 , X_2 , q , Y_6 , and Ring E are defined as above.

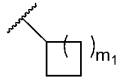
In another preferred embodiment, the compound has a structure represented by a formula selected from the following formulas:

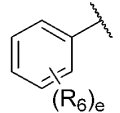
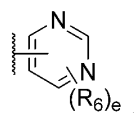
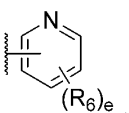


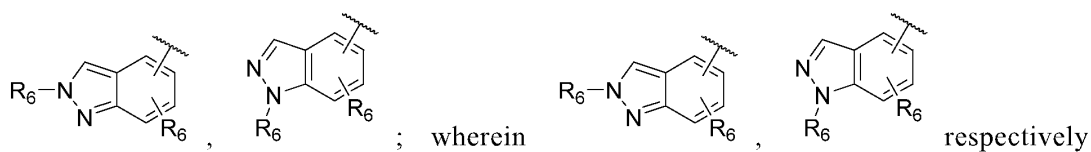
wherein R^2 , R^3 , R^5 , X_2 , q , Y_6 , and Ring E are defined as above.

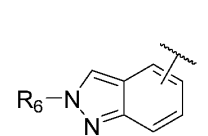
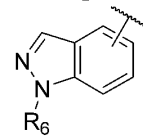
In another preferred embodiment, Ring E is selected from the group consisting of
 5 C_3 - C_6 cycloalkyl, 4 to 6-membered heterocyclyl, C_6 - C_{10} aryl, and 5 to 10-membered heteroaryl; wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^6 ;

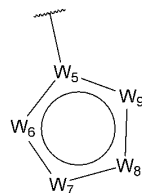
10 wherein, each R^6 is independently selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkynyl, C_2 - C_6 alkynyloxy, -CN, -OH, C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_5 - C_{10} heteroaryl.

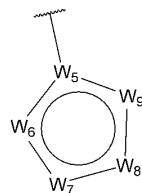
In another preferred embodiment, Ring E is  $_{m_1}$, wherein, $m_1 = 0, 1, 2, 3, 4$;

15 In another preferred embodiment, Ring E is  $_{(R_6)e}$,  $_{(R_6)e}$,  $_{(R_6)e}$,



represents that a hydrogen of any one of CH in ,  is independently substituted with a R⁶.



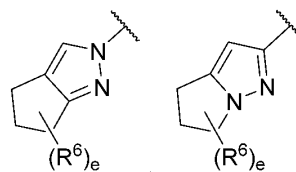
In another preferred embodiment, Ring E is , wherein, W₅, W₆, W₇, W₈, W₉, for each occurrence, is independently selected from CH, CD, N, O, S, N(R⁶), and CR⁶.

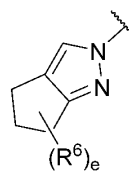
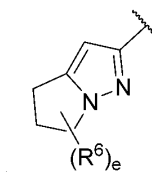
In another preferred embodiment, Ring E is a 5- to 9- membered heteroaryl, wherein the heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the heteroaryl are optionally substituted with 1 to 3 identical or different substituents R⁶;

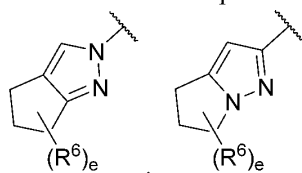
wherein each R⁶ is independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 3 to 8-membered heterocyclyl.

In another preferred embodiment, Ring E is a 5-membered heteroaryl having 2 nitrogen atoms; wherein the heteroaryl are optionally substituted with 1 to 3 identical or different substituents R⁶;

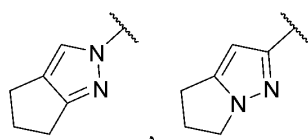
wherein each R⁶ is independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 3 to 8-membered heterocyclyl.



In another preferred embodiment, Ring E is , , wherein



respectively represents that e hydrogens of CH or CH₂ in

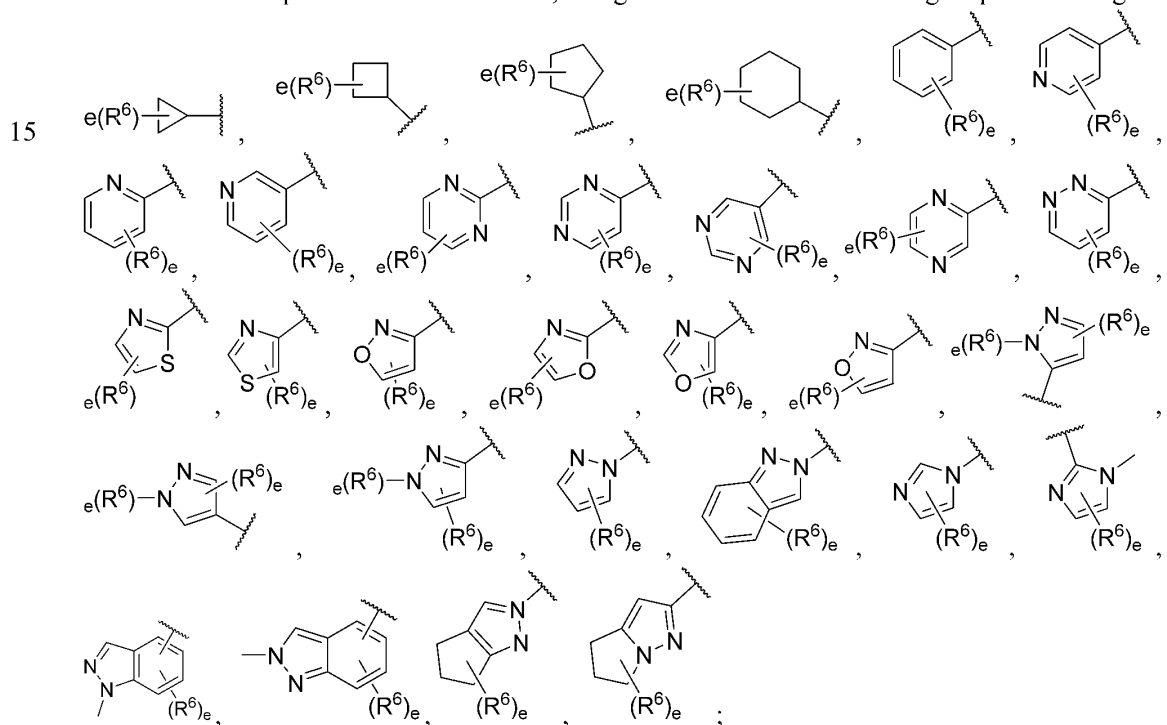


, are independently substituted with e identical or different substituents of R^6 ; e is 0, 1, 2, 3, 4, or 5.

In another preferred embodiment, Ring E is selected from the group consisting of C_3 - C_6 cycloalkyl, 4-6 membered heterocyclyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl, 5 pyrazolyl, indazolyl; wherein the cycloalkyl, heterocyclyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrazolyl, indazolyl are optionally substituted with 1 to 6 identical or different substituents R^6 ;

10 wherein, each R^6 is independently selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkynyl, C_2 - C_6 alkynyloxy, -CN, -OH, C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_5 - C_{10} heteroaryl.

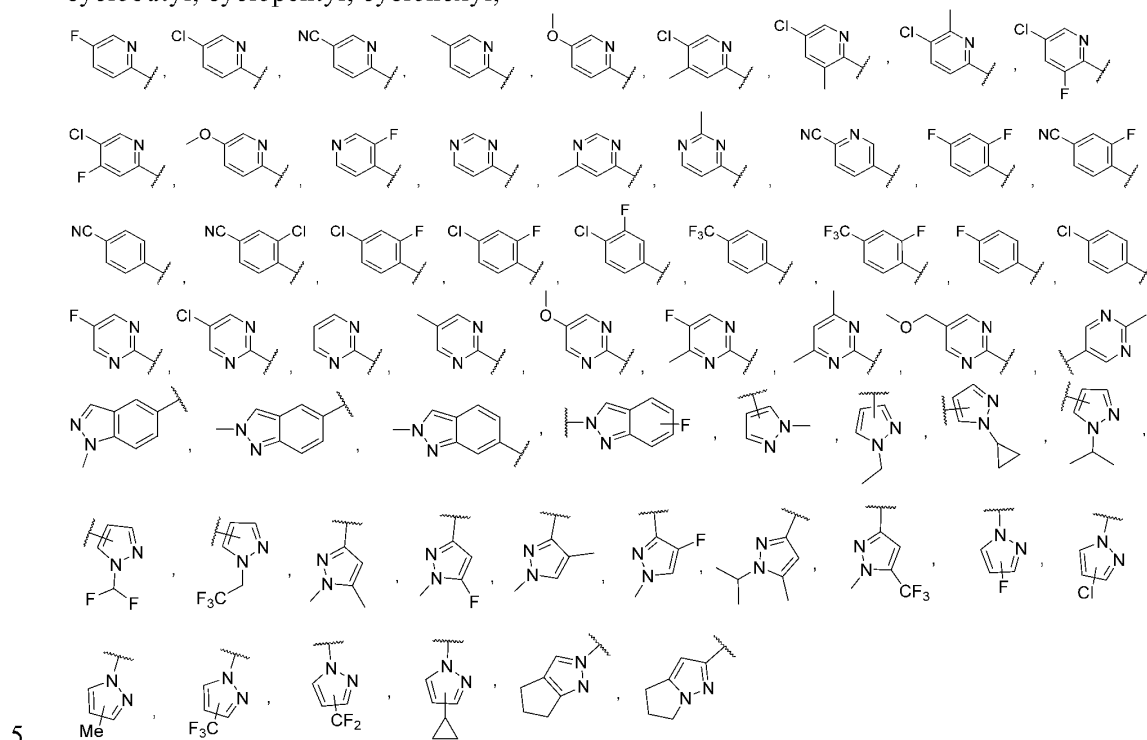
In another preferred embodiment, Ring E is selected from the group consisting of



20 wherein, each R^6 is independently selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, -CN, -OH, C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl.

e is 0, 1, 2, 3, 4, or 5;

more preferably, Ring E is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,



In another preferred embodiment, R^6 , for each occurrence, is independently selected from the group consisting of F, Cl, Br, methyl, ethyl, isopropyl, cyclopropyl, $-CF_3$, $-CHF_2$.

In another preferred embodiment, R^2 is F, Cl, Br, Me, $-CF_3$, $-CHF_2$.

10 In another preferred embodiment, R^2 is F, Cl, Br.

In another preferred embodiment, X_2 is a bond or $-CH_2-$.

In another preferred embodiment, R^3 is methyl, ethyl, cyclopropyl.

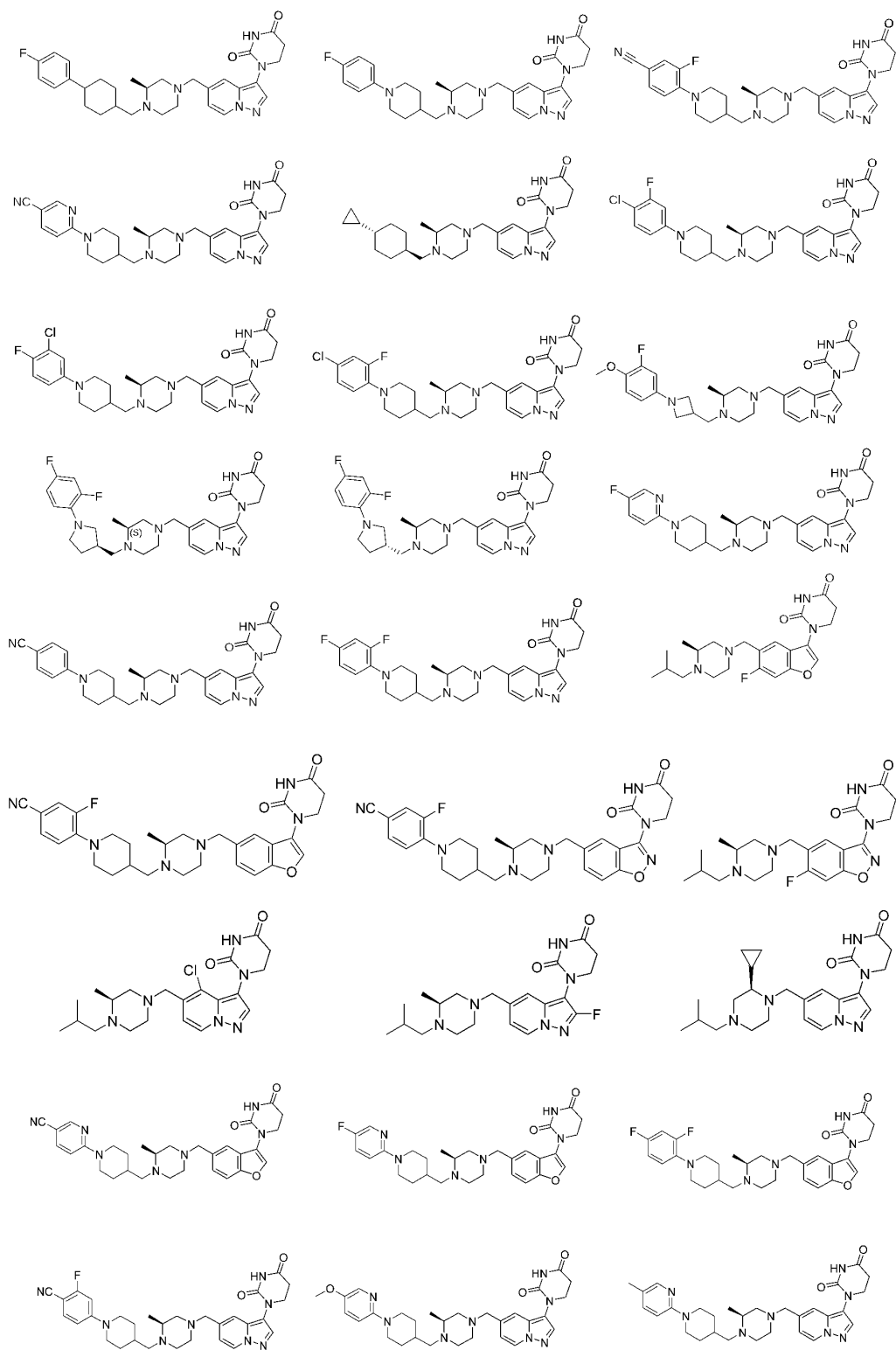
In another preferred embodiment, each R^5 is hydrogen, halogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl; preferably, each R^5 is hydrogen, F, Cl, Br, methyl, ethyl.

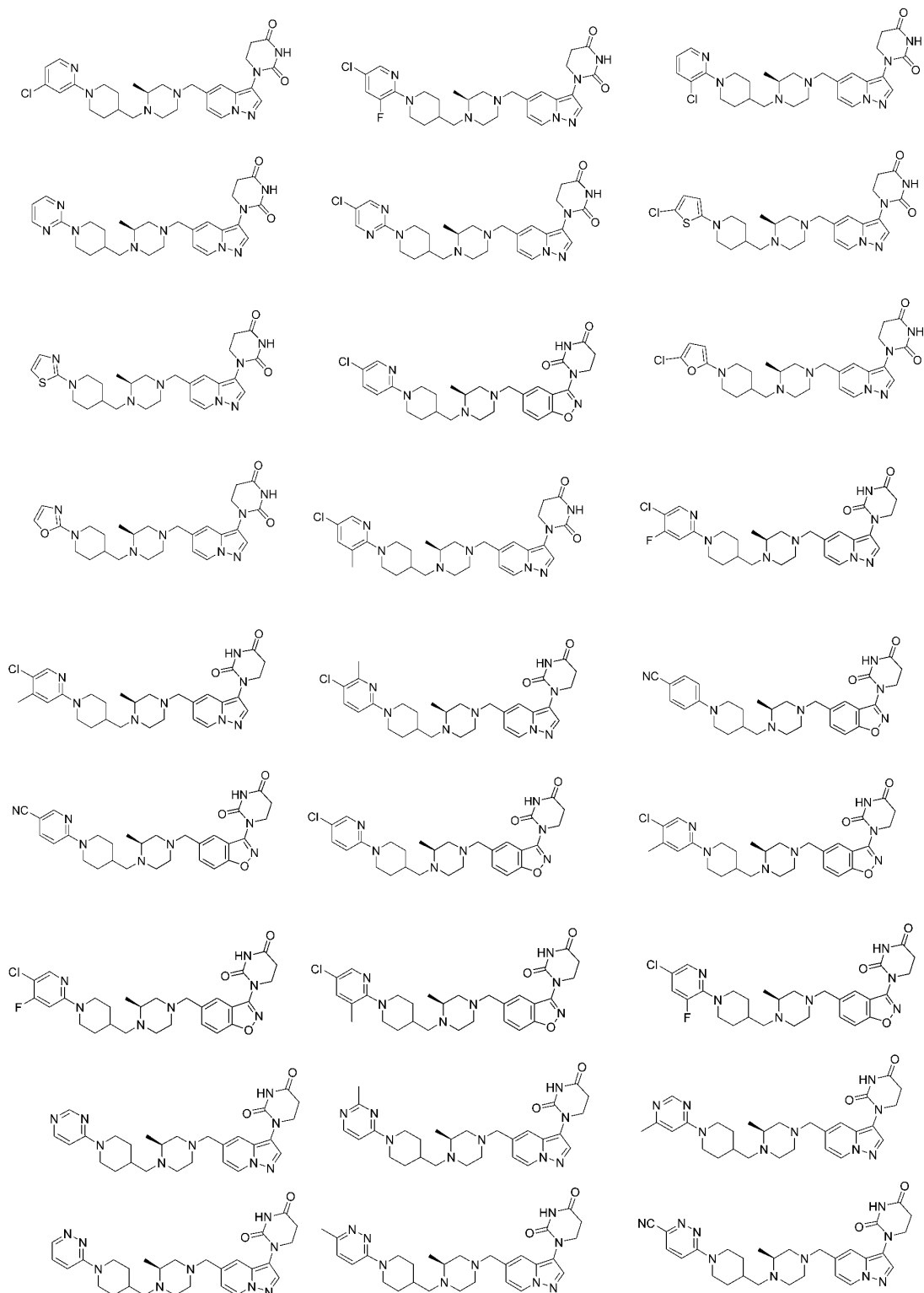
15 q is 0, 1, 2 or 3;

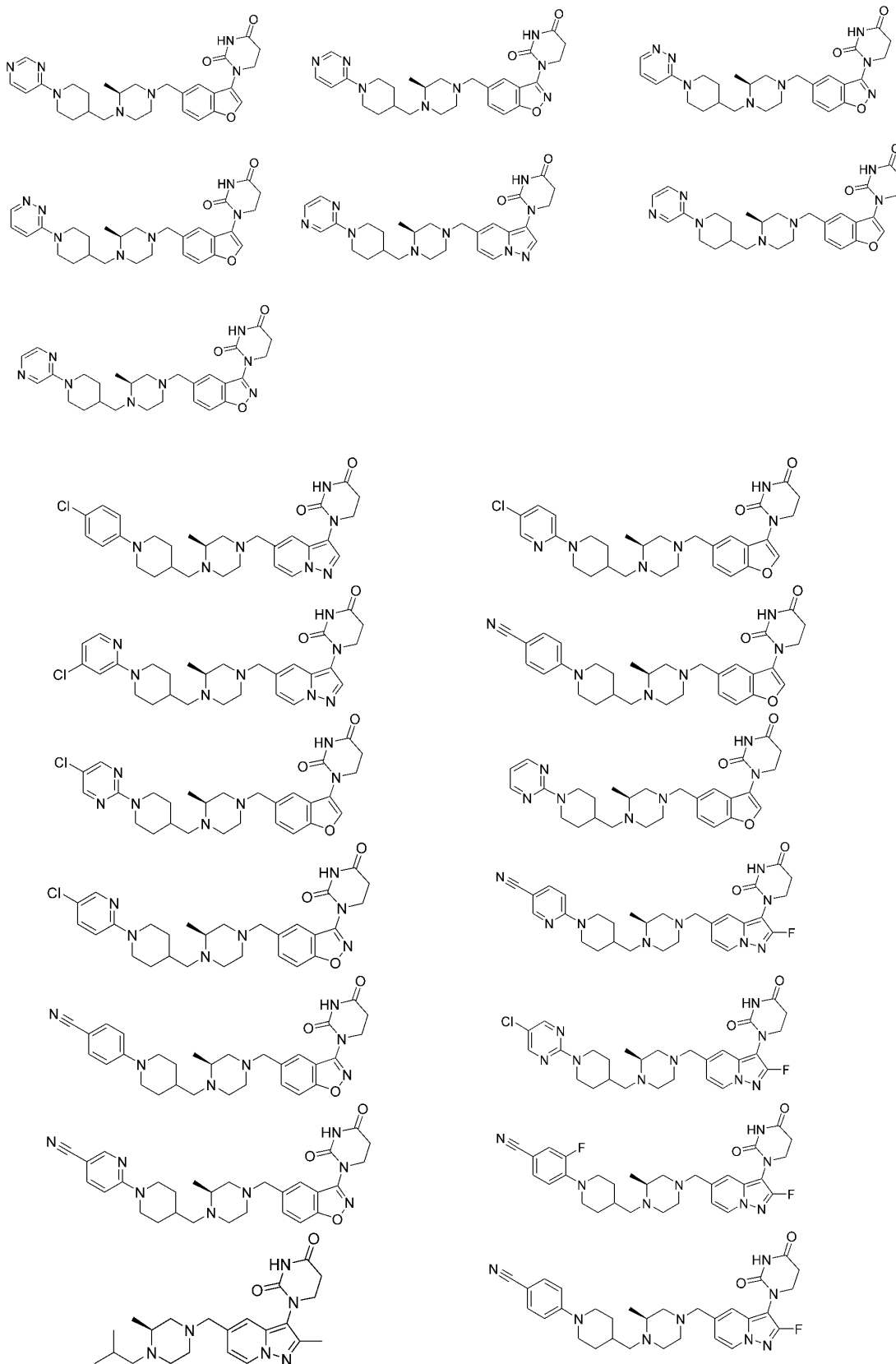
wherein when q is greater than or equal to 2, two R^5 are optionally taken together with atoms to which they are bound to form a carbocyclyl or heterocyclyl ring.

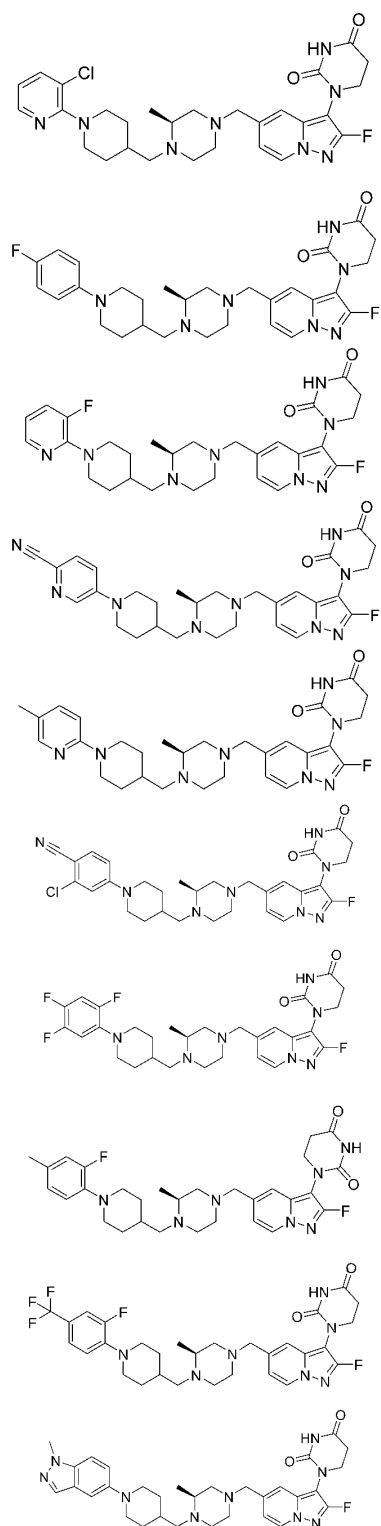
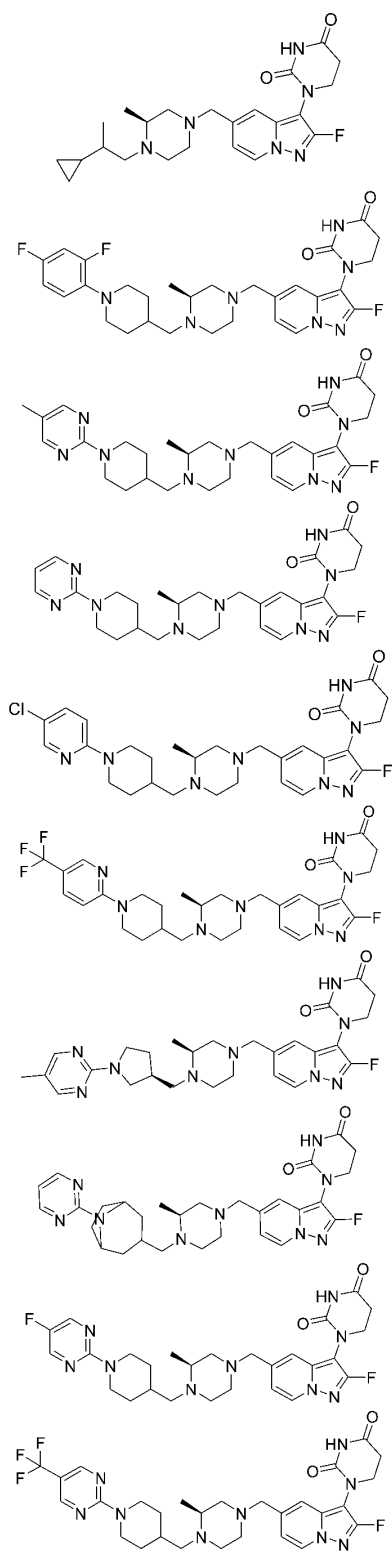
In another preferred embodiment, Y_6 is CH or N.

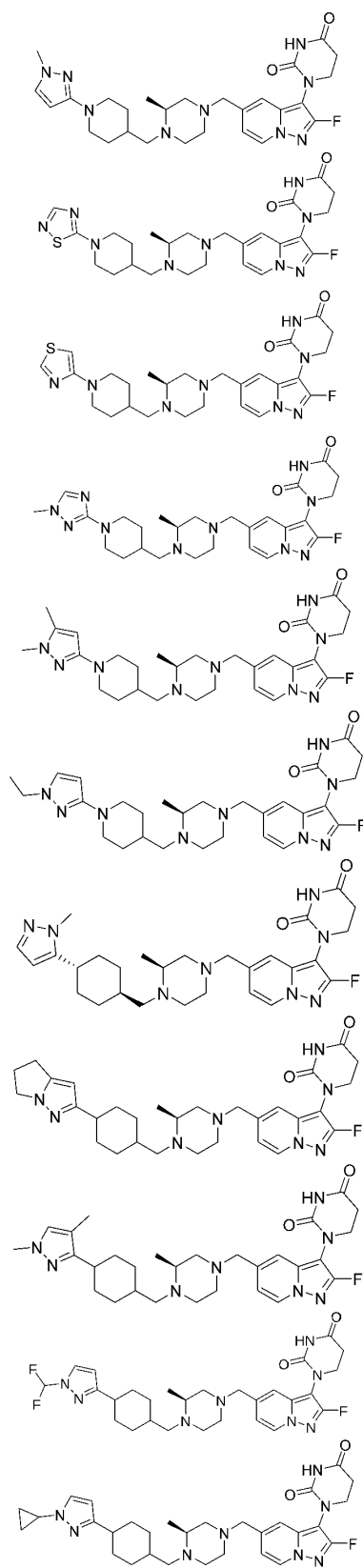
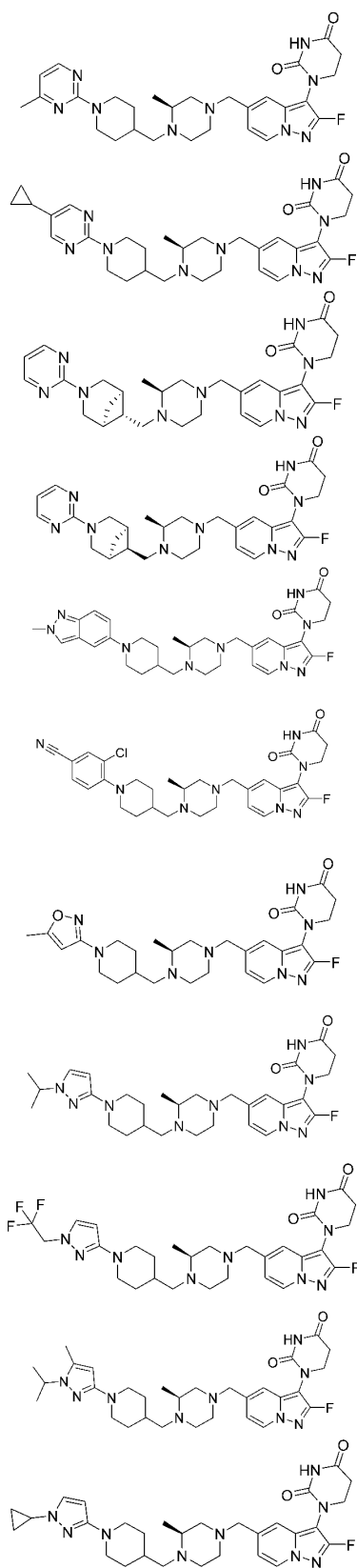
20 In another preferred embodiment, the compound is selected from the group consisting of:

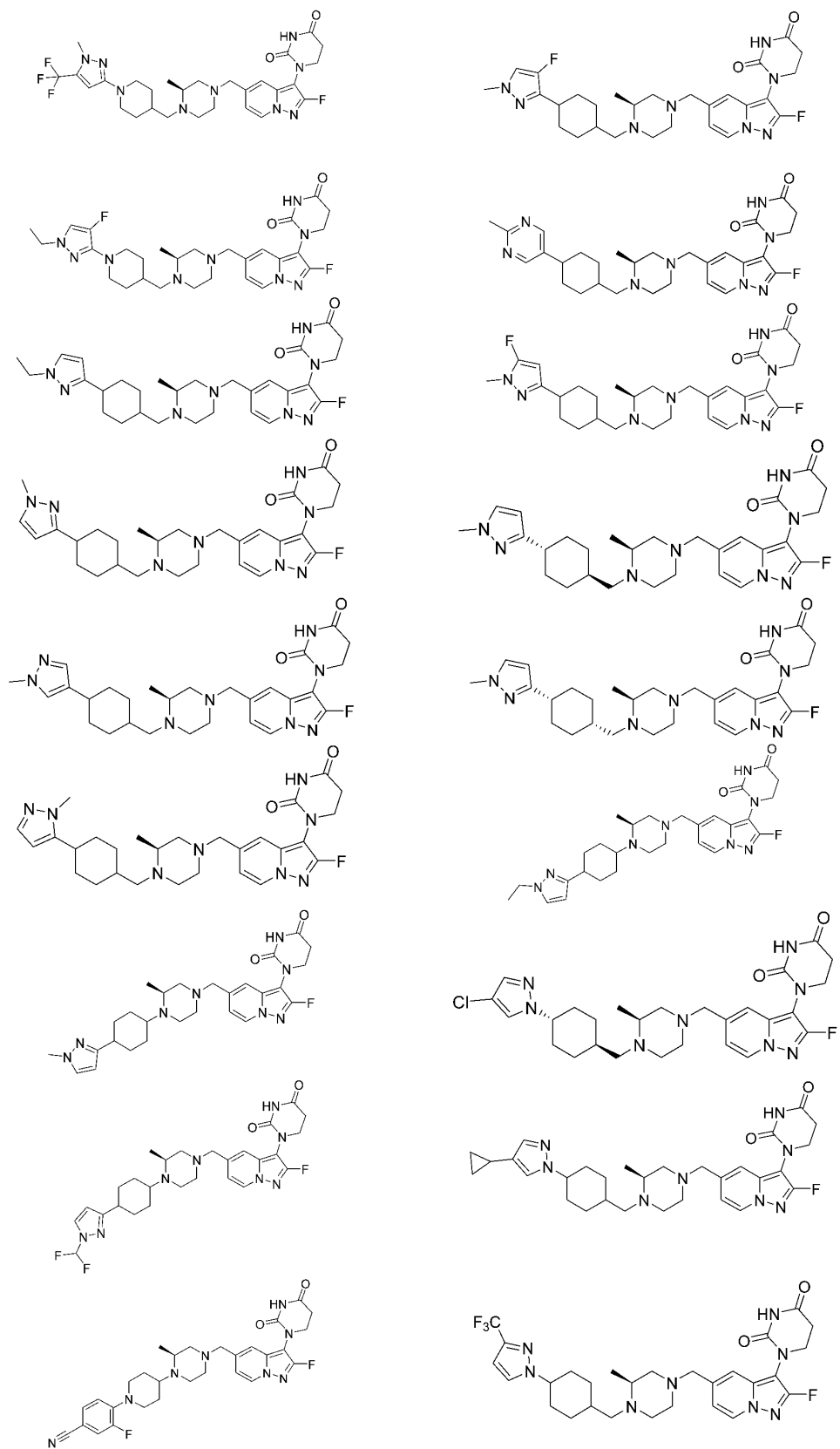


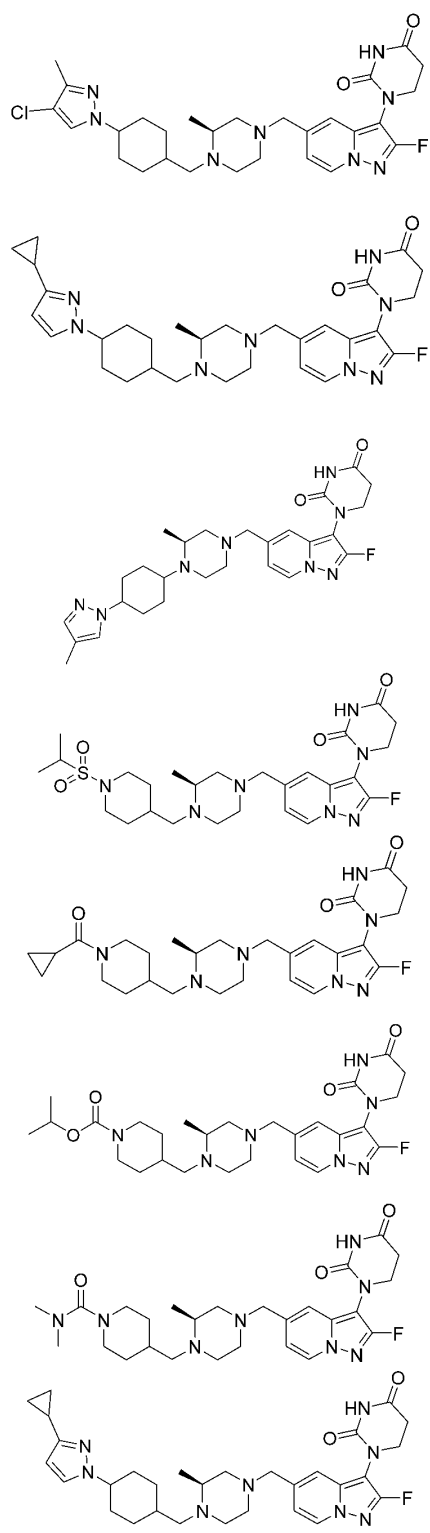
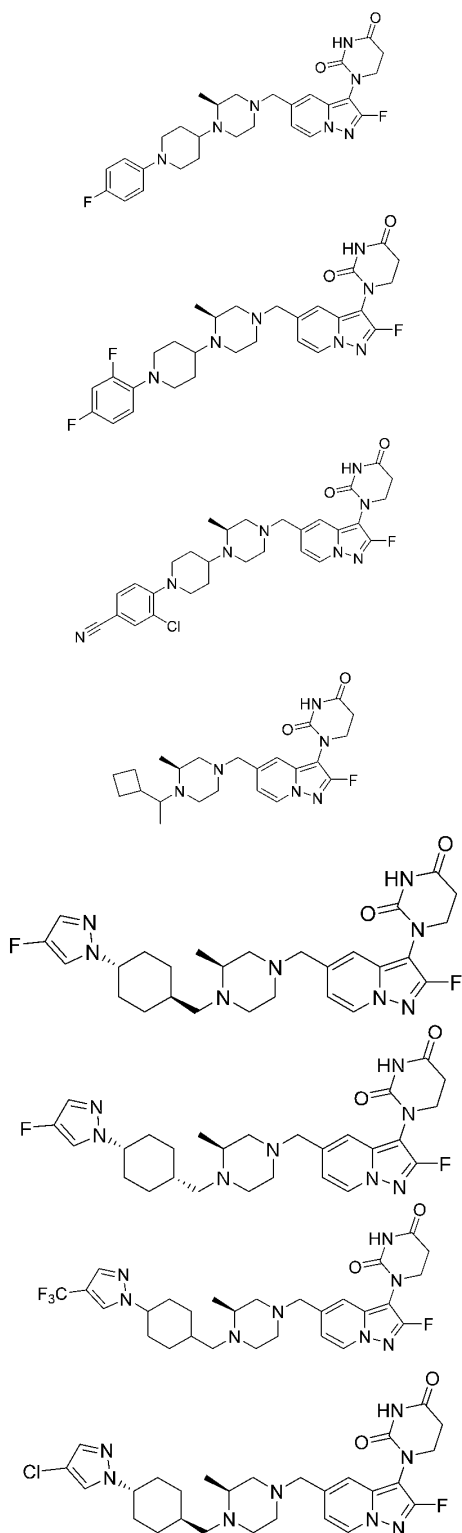


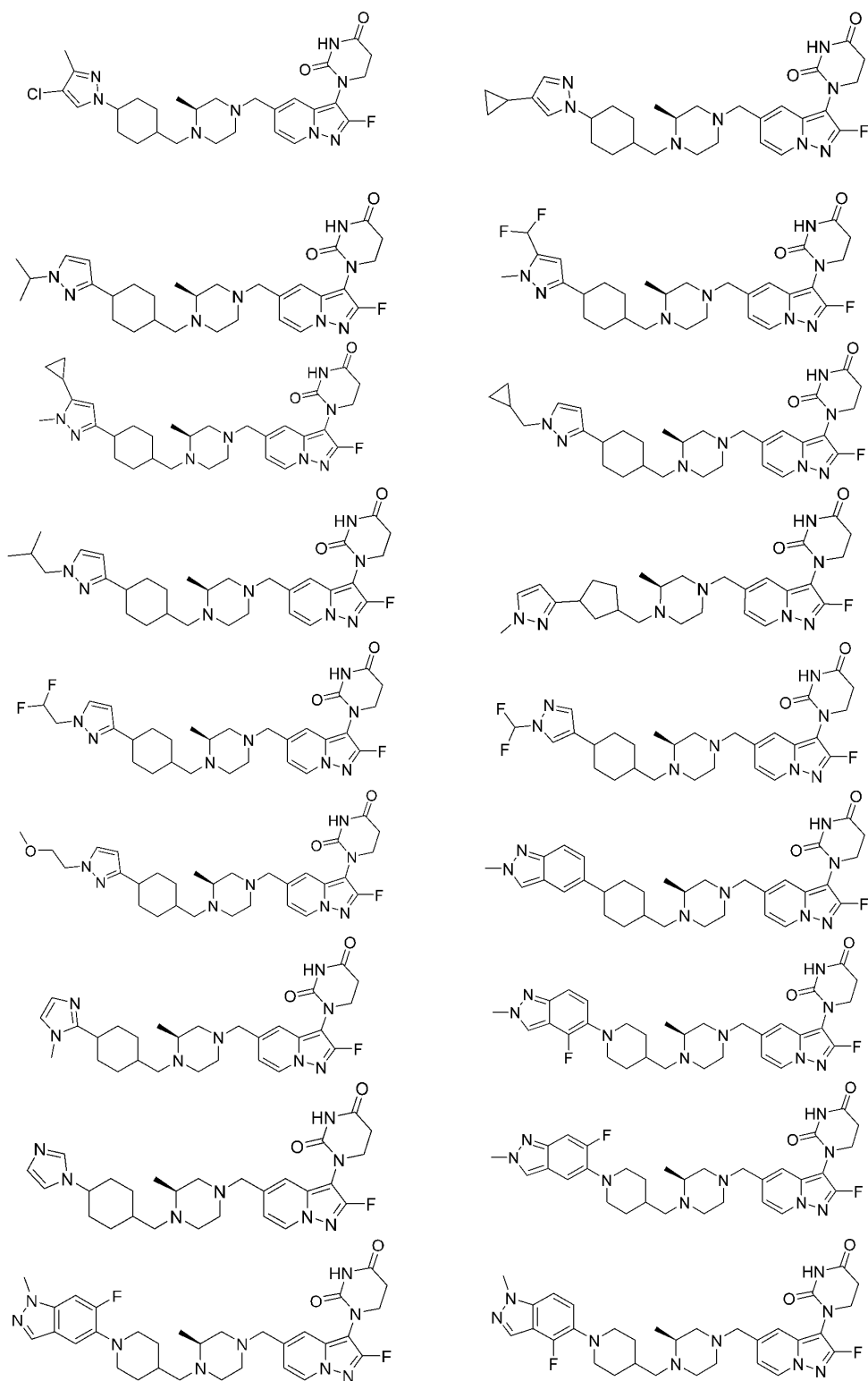


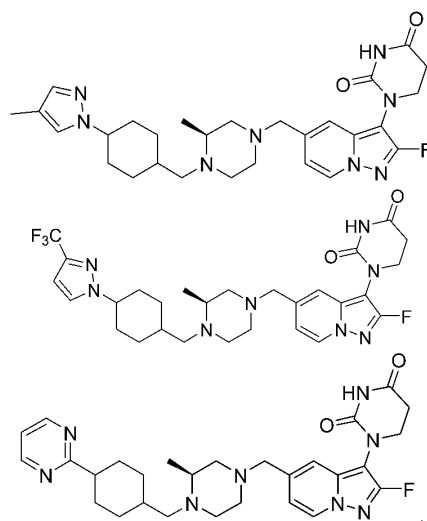
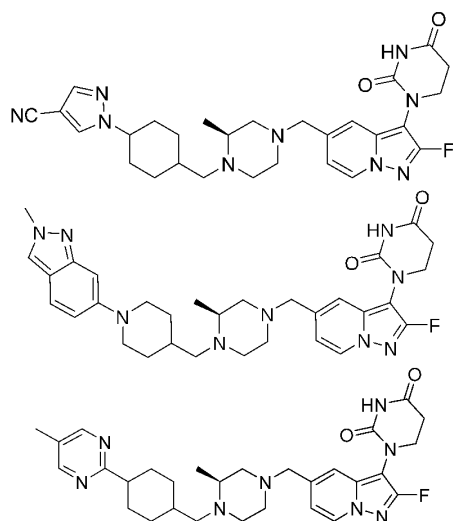




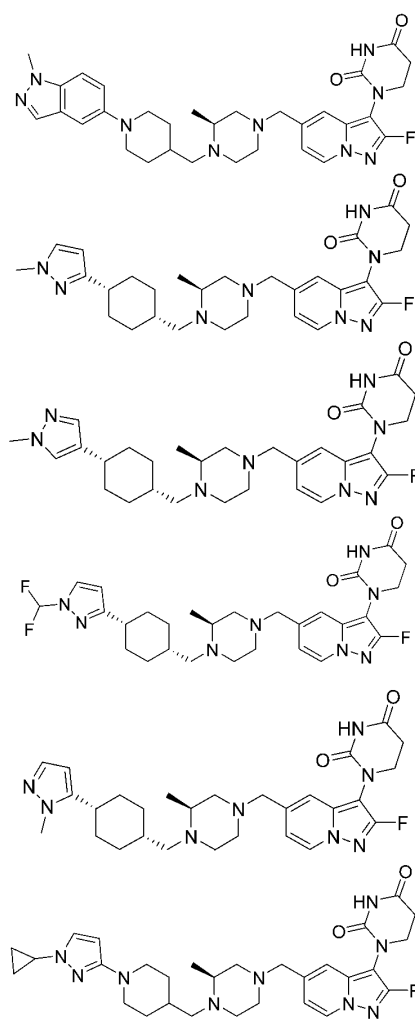
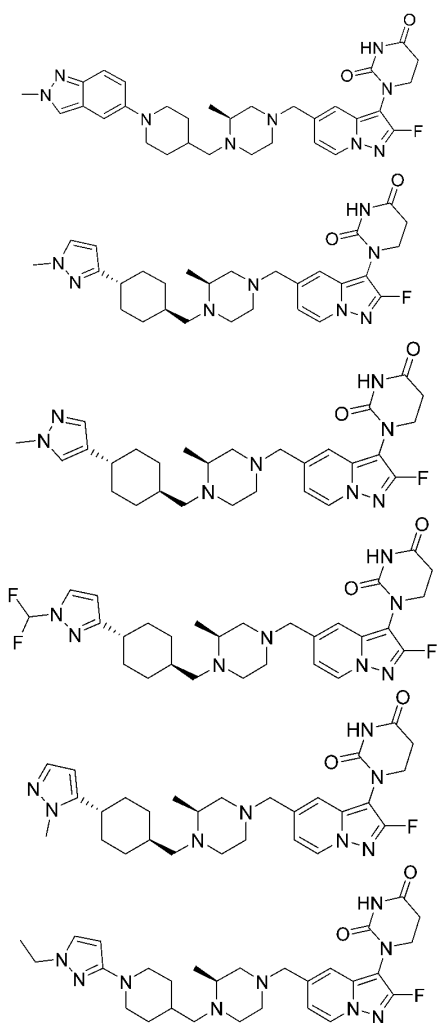


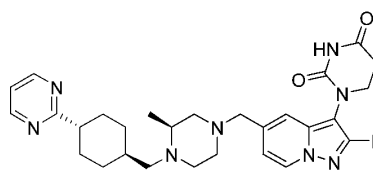
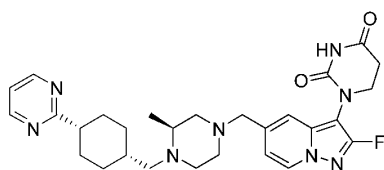






In another preferred embodiment, the compound is selected from the group consisting of:





In the second aspect, it provides a pharmaceutical composition comprising a compound of the first aspect of the present invention, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

5 In another preferred embodiment, the pharmaceutical composition is a tablet, a capsule, a granule, a syrup, a suspension, a solution, a dispersion, a slowed release preparation for oral or non-oral administration, an intravenous injection preparation, a subcutaneous injection preparation, an inhalation preparation, a transdermal preparation, a rectal or vaginal suppository.

10 In the third aspect, it provides a use of a compound of any one of the first aspect of the present invention or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof in the manufacture of a medicament for the treatment of a disease or disorder that is affected by the degradation of WIZ protein.

In another preferred embodiment, it provides a compound of the first aspect of the present invention, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the treatment of a disease or disorder affected by reactivating or increasing fetal hemoglobin expression in a subject in need thereof.

15 In the fourth aspect, it provides a method of inhibiting, reducing, or eliminating the activity of WIZ protein or WIZ protein expression in a subject in need thereof, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of the first aspect of the present invention or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In another preferred embodiment, wherein a disease or disorder includes sickle cell anemia, and beta-thalassemia.

25

DETAILED DESCRIPTION OF EMBODIMENTS

Terms

In the present invention, unless otherwise specified, the terms used have the general meanings known to those skilled in the art.

30 The term used herein, "alkyl" refers to a branched or straight chain saturated aliphatic hydrocarbon group. In one embodiment, the alkyl contains from 1 to about 12 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12) carbon atoms, more generally from 1 to about 6 carbon

atoms or from 1 to about 4 carbon atoms. In one embodiment, the alkyl contains from 1 to about 8 carbon atoms. In certain embodiments, the alkyl is C₁-C₂, C₁-C₃, or C₁-C₆. The specified ranges as used herein indicate an alkyl group having each member of the range described as an independent species. For example, the term C₁-C₆ alkyl as used herein indicates a straight or branched alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, tert-pentyl, neopentyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl and 2,3-dimethylbutyl. In one embodiment, the alkyl group is optionally substituted as described herein.

The term used herein, “alkenyl” refers to a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon double bonds that may occur at a stable point along the chain. Nonlimiting examples are C₂-C₆ alkenyl (such as C₂, C₃, C₄, C₅, C₆) and C₂-C₄ alkenyl. The specified ranges as used herein indicate an alkenyl group having each member of the range described as an independent species, as described herein for the alkyl moiety. Examples of alkenyl include, but are not limited to, ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl). In one embodiment, the alkenyl group is optionally substituted as described herein.

The term used herein, “alkynyl” refers to a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon triple bonds that may occur at any stable point along the chain, for example, C₂-C₆ alkynyl (such as C₂, C₃, C₄, C₅, C₆). The specified ranges as used herein indicate an alkynyl group having each member of the range described as an independent species, as described herein for the alkyl moiety. Examples of alkynyl include, but are not limited to, ethynyl, propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 4-hexyne and 5-hexyne. In one embodiment, the alkynyl group is optionally substituted as described herein.

The term used herein, “alkoxy” refers to an alkyl group as defined above with the indicated number of carbon atoms covalently bound through an oxygen bridge (-O-). Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Similarly an “alkylthio” or a “thioalkyl” group is an alkyl group as defined above with the indicated number of carbon atoms covalently bound through a sulfur bridge (-S-). Examples of thioalkyl include, but are not limited to, CH₃-S-, CH₃CH₂-S- and CH₃-S-CH₂-. In one embodiment, the alkoxy

group is optionally substituted as described herein.

The term used herein, “alkenyloxy” refers to an alkenyl group as defined above with the indicated number of carbon atoms covalently bound to the group it substitutes by an oxygen bridge (-O-).

5 The term used herein, “alkynyloxy” refers to an alkynyl group as defined above with the indicated number of carbon atoms covalently bound to the group it substitutes by an oxygen bridge (-O-).

10 The term used herein, “alkanoyl” refers to an alkyl group as defined above with the indicated number of carbon atoms covalently bound through a carbonyl (C=O) bridge. The carbonyl carbon is included in the number of carbons, that is C₂ alkanoyl is a CH₃(C=O)-group. In one embodiment, the alkanoyl group is optionally substituted as described herein.

15 The term used herein, “alkylester” refers to an alkyl group as defined with the indicated number of carbon atoms covalently bound through an ester linkage. The ester linkage may be in either orientation, e.g., a group of the formula -O(C=O) alkyl or a group of the formula -(C=O)O alkyl. Examples of alkylester include, but are not limited to, -O(C=O)CH₃, -O(C=O)CH₂CH₃, -(C=O)OCH₃, -(C=O)OCH₂CH₃.

20 The term used herein, “cycloalkyl” refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term “cycloalkyl” includes cycloalkenyl groups (i.e. the cyclic group having at least one double bond). As used herein, C₃-C₈ cycloalkyl is constructed by 3 to 8 ring carbon atoms (such as, 3, 4, 5, 6, 7 or 8 ring carbon atoms). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and partially unsaturated groups such as cyclopentenyl and cyclohexenyl.

25 The term used herein, “amide” or “carboxamide” refers to -C(O)NR^cR^d, wherein R^c and R^d are each independently selected from hydrogen, alkyl, for example, C₁-C₆ alkyl, alkenyl, for example, C₂-C₆ alkenyl, alkynyl, for example, C₂-C₆ alkynyl, -C₀-C₄ alkyl (C₃-C₇ cycloalkyl), -C₀-C₄ alkyl (C₃-C₇ heterocycloalkyl), -C₀-C₄ alkyl(aryl), and -C₀-C₄alkyl (heteroaryl); or together with the nitrogen to which they are bonded, R^c and R^d
30 can form a C₃-C₇ heterocyclic ring. In one embodiment, the R^c and R^d groups are each independently optionally substituted as described herein.

35 The term used herein, “haloalkyl” refers to both branched and straight-chain alkyl groups substituted with 1 or more halogen atoms, up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, monofluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

The term used herein, “haloalkoxy” refers to a haloalkyl group as defined herein attached through an oxygen bridge (oxygen of an alcohol radical).

The term used herein, “halo” or “halogen” refers to independently any of fluoro, chloro, bromo, and iodo.

5 The term used herein, “aryl” refers to aromatic groups containing only carbon in the aromatic ring or rings. In one embodiment, the aryl groups contain 1 to 3 separate or fused rings and 6 to about 10 ring atoms (i.e. C₆-C₁₀, such as 6, 7, 8, 9, 10 ring atoms), without heteroatoms as ring members. When indicated, such aryl groups may be further substituted with carbon or non-carbon atoms or groups. Such substitution may include fusion to a 5 to
10 7-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N, O, and S, to form, for example, a 3,4-methylenedioxyphenyl group. Aryl groups include, for example, phenyl, naphthyl, including 1-naphthyl and 2-naphthyl, fluorenyl, and anthryl. In one embodiment, aryl groups are pendant. An example of a pendant ring is a phenyl group substituted with a
15 phenyl group. In one embodiment, the aryl group is optionally substituted as described herein.

The term used herein, “heterocyclyl” refers to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring without aromaticity) monocyclic or bicyclic radical of 4, 5, 6, 7, 8, 9, or 10 ring atoms in which at least one ring
20 atom is a heteroatom selected from nitrogen, oxygen, and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described above. In one embodiment, the only heteroatom is oxygen. A heterocyclyl may be a monocycle having 4 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, and S) or a bicycle having 6 to 10 ring members (4 to
25 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. In one embodiment, the only heteroatom is sulfur. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, piperidonyl, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl,
30 azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, dihydroisoquinoliny, tetrahydroisoquinoliny, pyrazolidiny, imidazolidiny, 2-oxa-5-azabicyclo[2.2.2]octane,
35 3-oxa-8-azabicyclo[3.2.1]octane, 8-oxa-3-azabicyclo[3.2.1]octane,

6-oxa-3-azabicyclo[3.1.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl, quinoliziny, N-pyridyl ureas, and pyrrolopyrimidine. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 1 or 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxothiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

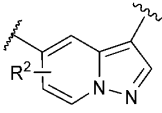
The term used herein, "heteroaryl" can be a stable monocyclic aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5- to 7-membered aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. The 5 to 10 membered heteroaryl described herein may contain 5, 6, 7, 8, 9 or 10 ring atoms. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. Monocyclic heteroaryl groups typically have from 5 to 7 ring atoms. In some embodiments bicyclic heteroaryl groups are 9- to 10-membered heteroaryl groups, that is, groups containing 9 or 10 ring atoms in which one 5- to 7-member aromatic ring is fused to a second aromatic or nonaromatic ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. In one embodiment, the total number of S and O atoms in the heteroaryl group is not more than 2. In another embodiment, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, pyridinyl (including, for example, 2-pyridinyl, 2-hydroxypyridinyl, 3-pyridinyl, 3-hydroxypyridinyl, 4-pyridinyl, 4-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinoliny, isoquinoliny, tetrahydroisoquinoliny, indolyl, benzimidazolyl, benzofuranyl, cinnoliny, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothioophenyl, benzothiazolyl, benzoxazolyl, quinazoliny, quinoxaliny, naphthyridinyl, tetrahydrofuranly, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein.

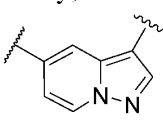
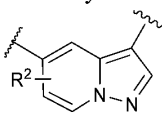
The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a moiety selected from the indicated group,

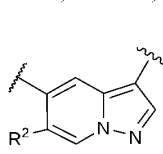
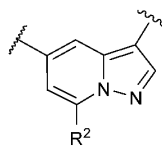
provided that the designated atom's normal valence is not exceeded.

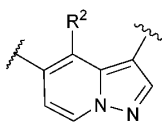
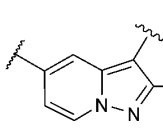
Unless otherwise stated, it is assumed that any heteroatom with a lower valence state has enough hydrogen atoms to replenish its valence state.

When a Ring system is substituted with a substituent, it means that the substituent is attached to an aromatic or nonaromatic ring system and replaces an available hydrogen on

the ring system. Particularly,  represents that a hydrogen of any one of CH

in the ring system of  is substituted with a R², that is,  has a

formula selected from the group consisting of , ,

, , wherein R² is as defined above.

10 **Active ingredient**

As used herein, "the compound of the present invention" refers to the compound represented by the formula I, and further comprises the pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

The salt of the compound in the present invention may be formed which is also within the scope of the present invention. Unless otherwise stated, the compound in the present invention is understood to include its salt. The term "salt" as used herein refers to a salt formed in the form of acid or base from inorganic or organic acid and base. Further, when the compound in the present invention contains a base fragment which includes, but is not limited to pyridine or imidazole, when contains an acid segment which includes, but is not limited to carboxylic acid. The zwitter-ion that may form "inner salt" is included within the range of the term "salt". Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salt is preferred, although other salts are also useful and may be used, for example, in the separation or purification steps of the preparation process. The compound of the present invention may form a salt, for example, compound I is reacted with a certain amount (such as an equivalent amount) of an acid or base, and precipitated in a medium, or freeze-dried in aqueous solution.

The compounds in the present invention containing base fragments which include but are not limited to amines or pyridine or imidazole rings, may form salt with organic or

inorganic acid. Typical acids that form salts include acetate (e.g., acetate or trihalogenated acetic acid, e.g., trifluoroacetic acid), adipate, alginate, ascorbate, aspartate, benzoate, benzene sulfonate, disulfate, borate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentane propionate, diethylene glycolate, lauryl sulfate, ethanesulphonate, fumarate, 5 gluceptate, glycerophosphate, hemisulphate, enanthate, caproate, hydrochloride, hydrobromide, hydriodate, isethionate(e.g., 2-hydroxy-ethesulfonate), lactate, maleate, mesylate, naphthalenesulfonate (e.g., 2-naphthalenesulfonate), nicotinate, nitrate, oxalate, pectate, persulfate, phenylpropionate (e.g., 3-phenylpropionate), phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate (e.g., formed with sulfuric acid), 10 sulfonate, tartrate, thiocyanate, toluenesulfonate(e.g., tosylate), dodecanoate, etc.

Some compounds of the invention may contain acidic fragments including, but not limited to carboxylic acid may form salts with various organic or inorganic bases. Salts formed by typical bases includes ammonium salt, alkali metal salt (such as sodium, lithium and potassium salts), alkaline earth metal salt (such as calcium and magnesium 15 salts), and salts formed by organic bases (e.g., organic amines), such as benzathine, dicyclohexylamine, hydrabamine (salt formed with N,N-bis(dehydroabietyl) ethylenediamine), *N*-methyl-D-glucanamine, *N*-methyl-D-glucoamide, tert-butylamine, and the salts formed with amino acids such as arginine, lysine, etc. Basic nitrogen-containing groups can form quaternary ammonium salts with halides, such as 20 small molecular alkyl halides (e.g., chlorides, bromides and iodides of methyl, ethyl, propyl and butyl), dialkyl sulfates (such as dimethyl, diethyl, dibutyl, and dipentyl sulfates), long chain halides (e.g., chlorides, bromides and iodides of decyl, dodecyl, tetradecyl, and tetradecyl), aralkyl halides (such as bromides of benzyl and phenyl), etc.

The prodrug and solvate of the compound in the present invention are also included 25 within the scope of the present invention. The term "prodrug" herein refers to a compound resulting from the chemical transformation of a metabolic or chemical process to produce a compound, salt, or solvate in the present invention for the treatment of an associated disease. The compounds of the invention include solvates such as hydrates.

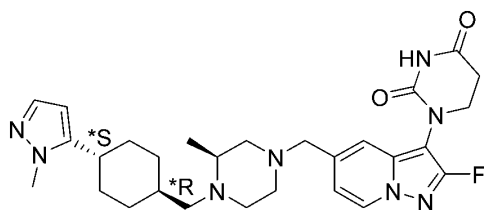
Compound, salt or solvate in the present invention, may be present in tautomeric 30 forms such as amide and imino ether. All of these tautomers are part of the present invention.

Stereoisomers of all compounds (e.g., those asymmetric carbon atoms that may be present due to various substitutions), including their enantiomeric forms and non-enantiomeric forms, all belong to the protection scope of the present invention. The 35 independent stereoisomer in the present invention may not coexist with other isomers (e.g.,

as a pure or substantially pure optical isomer with special activity), or may be a mixture (e.g., racemate), or a mixture formed with all other stereoisomers or a part thereof. The chiral center of the present invention has two configurations of S or R, which is defined by International Union of Pure and Applied Chemistry (IUPAC) founded in 1974. The racemization form can be solved by physical methods, such as fractional crystallization, or separation crystallization by derivation into diastereomers, or separation by chiral column chromatography. Individual optical isomer can be obtained from racemate by appropriate methods, including but not limited to conventional methods, such as recrystallization after salting with optically active acids.

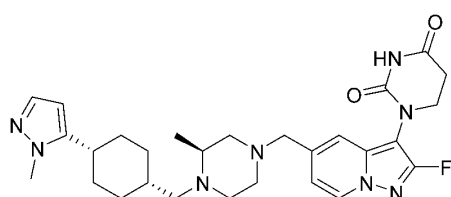
When a stereocenter is designated as “*R” or “*S”, it means that the absolute stereochemistry for such a stereocenter is undetermined (even if the bonds are drawn stereo specifically) although it is in a substantially single steric configuration. In other word, “*R” can be absolute R configuration, or absolute S configuration. Similarly, “*S” can be absolute R configuration, or absolute S configuration. “*R” or “*S” is assigned randomly for such molecules. A stereocenter designated as “*R” can be in a single steric configuration same as or different from that of another stereocenter designated as “*S”. A stereocenter designated as “*R” can be in a single steric configuration same as or different from that of another stereocenter designated as “*R”. A stereocenter designated as “*S” can be in a single steric configuration same as or different from that of another stereocenter designated as “*S”.

For example, it will be clear that the absolute stereochemistry of Compound 102-B

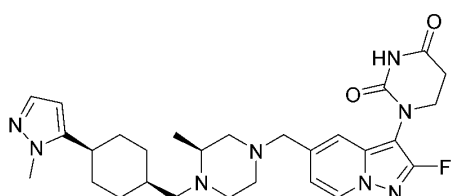
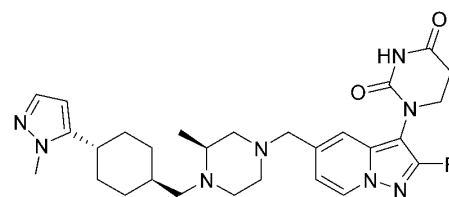


Compound 102-B

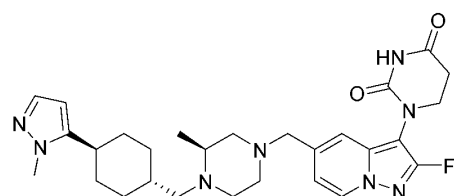
is undetermined and has one of the following structure formulae



or

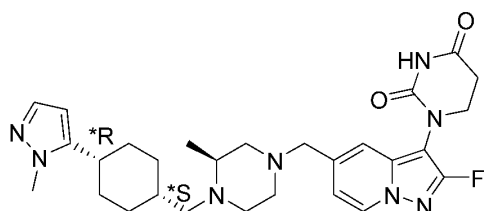


or



;

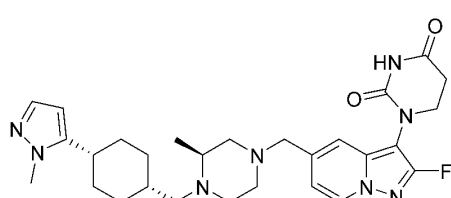
while the absolute stereochemistry of Compound 102-A



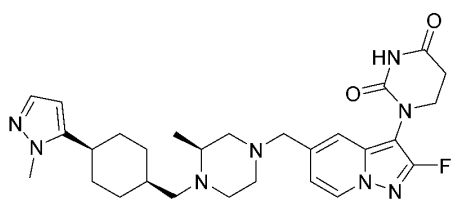
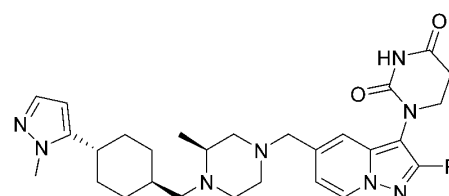
Compound 102-A

is undetermined and has one of the following

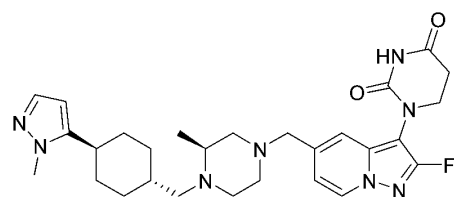
structure formulae except the absolute stereochemistry of Compound 102-B:



or



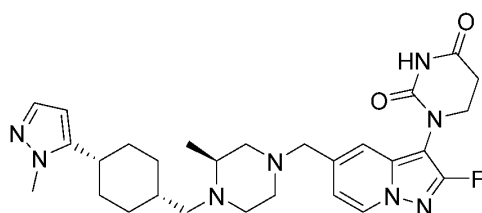
or



;

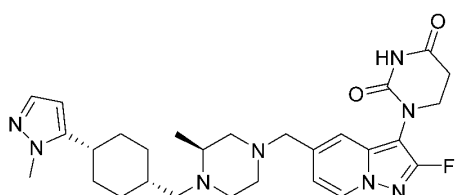
5

while the absolute stereochemistry of Compound 102-A'

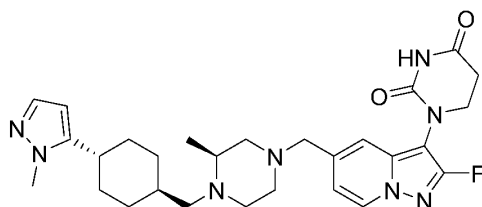


Compound 102-A'

following



while the absolute stereochemistry of Compound 102-B'

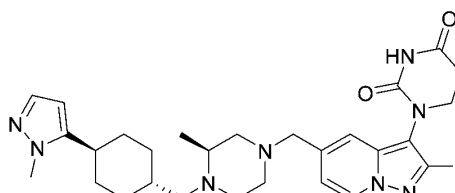


Compound 102-B'

5

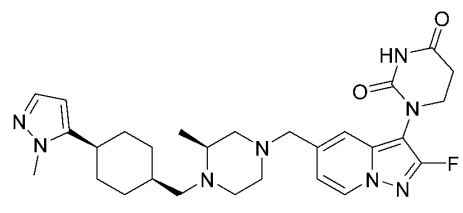
the

following



.

or



;

is determined as a cis isomer and has one of the structure formulae:

is determined as a trans isomer and has one of the structure formulae:

10 Weight content of compound in the present invention obtained by preparation, separation and purification in turn is equal to or greater than 90%, such as equal to or greater than 95%, equal to or greater than 99% ("very pure" compound), and listed in the description of the text. In addition, the "very pure" compound of the present invention is also part of the present invention.

15 All configuration isomers of the compound of the present invention are within the scope, whether in mixture, pure or very pure form. The definition of the compound of the present invention comprises cis (*Z*) and trans (*E*) olefin isomers, and cis and trans isomers

of carbocyclic and heterocyclic.

In the entire specification, the groups and substituents can be selected to provide stable fragments and compounds.

Specific functional groups and chemical term definitions are described in detail. For the purposes of the present invention, the chemical elements are consistent with Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed. The definition of a particular functional group is also described. In addition, the basic principles of Organic Chemistry as well as specific functional groups and reactivity described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, the entire content of which is incorporated herein by reference.

Some compounds of the present invention may exist in specific geometric or stereoisomer forms. The present invention covers all compounds, including their cis and trans isomers, R and S enantiomers, diastereomers, (D) type isomers, (L) type isomers, racemic mixtures and other mixtures. In addition, asymmetric carbon atom can represent substituent, such as alkyl. All isomers and mixtures thereof are included in the present invention.

According to the invention, mixtures of isomers may contain a variety ratio of isomers. For example, mixtures with only two isomers may have the following combinations: 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0, all ratios of the isomers are within the scope of the present invention. Similar ratio and the ratio of mixtures of more complex isomers, which are readily understood by general skill of the art are also within the scope of the invention.

The present invention also includes the isotope labeled compound, which is equivalent to the original compound herein. However, in fact, the substitution of one or more atoms by an atom with a different atomic weight or mass number usually occurs. Examples of compound isotopes that may be listed in the present invention include hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine isotopes such as ²H, ³H, ¹³C, ¹¹C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F and ³⁶Cl, respectively. Compound, or enantiomer, diastereomer, isomer, or pharmaceutically acceptable salt or solvate, the above compound containing isotopes or other isotope atoms are all within the scope of the invention. Some isotope-labeled compounds in the present invention, such as the radioactive isotopes of ³H and ¹⁴C, are also included and are useful in experiments on the tissue distribution of drugs and substrates. Tritium (³H) and Carbon-14 (¹⁴C), which are relatively easy to prepare and detect. In addition, heavier isotope substitutions such as deuterium, i.e. ²H, have advantages in certain therapies due to their good metabolic

stability, such as increased half-life or reduced dosage in vivo, and thus may be preferred in certain situations. Isotope-labeled compounds can be prepared by conventional methods through replacing readily available isotope-labeled reagents with non-isotopic reagents that can be prepared using the disclosed scheme shown in the Example.

5 If the synthesis of the compound of the invention is to be designed, it can be prepared by asymmetric synthesis, or derivatized with chiral auxiliary reagent, separating the resulting diastereomeric mixture and removing the chiral adjunct to obtain a pure enantiomer. In addition, if a molecule contains a basic functional group, such as an amino acid, or an acidic functional group, such as a carboxyl group, a diastereomer can be
10 formed with a salt of suitable optically active acids or bases, which can be separated by conventional means, such as crystallization or chromatography, to obtain a pure enantiomer.

As described herein, the compound in the present invention may be substituted with any number of substituents or functional groups to extend its scope. In general, whether
15 the term "substituted" appears before or after the term "optional", the general formula that includes substituents in the compound of the present invention means the substitution of a specified structural substituent for a hydrogen radical. When multiple locations in a particular structure are replaced by multiple specific substituents, each location of the substituents can be the same or different. The term "substituted" as used herein includes
20 all substitution that allows organic compounds to be substituted. Broadly speaking, the allowable substituents include non-annular, cyclic, branched, non-branched, carbocyclic and heterocyclic, aromatic ring and non-aromatic organic compounds. In the present invention, such as heteroatomic nitrogen, its valence state may be supplemented by a hydrogen substituent or by any permitted organic compound described above. Furthermore,
25 the invention is unintentionally limited to the substituted organic compounds. The present invention considers that a combination of substituents and variable groups is good for the treatment of diseases (such as infectious or hypertrophic diseases) in the form of stable compounds. The term "stable" herein refers to a stable compound which is sufficient for maintaining the integrity of the compound structure within a sufficiently long time,
30 preferably in a sufficiently long time, which is hereby used for the above purposes.

The metabolites of the compounds of the present application and their pharmaceutically acceptable salts, and prodrugs that can be converted into the compounds of the present application and their pharmaceutically acceptable salts in vivo, also included in the claims.

35

Preparation method

The preparation method of the compound of the formula (I) of the present invention is more specifically described below, but these specific methods do not constitute any limitation of the invention. The compound of the invention may also optionally be
5 conveniently prepared by combining the various synthetic methods described in this specification or known in the art, such a combination may be easily performed by a skilled person in the art to which the invention belongs.

Pharmaceutical composition and method of administration

10 The pharmaceutical compositions of the present invention are used to prevent and / or treat a disease or disorder that is affected by the degradation of WIZ protein, such as sickle cell disease, beta-thalassemia, anemia, or related hemoglobinopathy.

The compounds of the formula (I) may be used in combination with other drugs known to treat or improve similar conditions. When administered in combination, the
15 original administration for the drug can remain unchanged, while compound of formula I may be administered simultaneously or subsequently. Pharmaceutical composition containing one or more known drugs and the compound of formula I may be preferred when administered in combination with one or more other drugs. The drug combination also includes administering the compound of formula I and other one or more known drugs
20 at overlapping time. When the compound of formula I is combined with other one or more drugs, the dose of the compound or known drug may be lower than that of their individual use.

The dosage forms of the pharmaceutical composition of the present invention include (but are not limited to): injection, tablet, capsule, aerosol, suppository, pellicle, pill,
25 liniment for external use, controlled release or sustained-release or nano formulation.

The pharmaceutical composition of the present invention comprises a compound of the present invention or a pharmaceutically acceptable salt and a pharmaceutically acceptable excipient or carrier with safe and effective amount. wherein "safe and effective amount" refers to the amount of compound is sufficient to significantly improve the
30 condition, not to produce severe side effects. Typically, the pharmaceutical composition contains 1-2000 mg of the compound / dosage of the present invention, and preferably contains 1-1000 mg of the compound / dosage of the present invention. Preferably, "one dosage" is a capsule or a pill.

"Pharmaceutically acceptable carrier" refers to one or more compatible solid or liquid
35 filler or gel substances, which are suitable for human use, and must be sufficiently pure

and of sufficiently low toxicity. "Compatible" herein refers to the ability of each component of a composition can be mixed with the compound of the present invention and can be mixed with each other without appreciably reducing the efficacy of the compound. Examples of pharmaceutically acceptable carrier include cellulose and derivatives thereof
5 (such as sodium carboxymethylcellulose, sodium ethylcellulose, cellulose acetate, etc.), gelatin, talc, solid lubricant (such as stearic acid, magnesium stearate), calcium sulfate, vegetable oil (such as soybean oil, sesame oil, peanut oil, olive oil, etc.), polyol (such as propylene glycol, glycerol, mannitol, sorbitol, etc.), emulsifier (such as Tween®), wetting agent (such as lauryl sodium sulfate), colorant, flavoring, stabilizer, antioxidant,
10 preservative, pyrogen-free water, etc.

There is no special limitation of administration mode for the compound or pharmaceutical compositions of the present invention, and the representative administration mode includes (but is not limited to): oral, intratumorally, rectal, parenteral (intravenous, intramuscular or subcutaneous), and topical administration.

15 Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In these solid dosage forms, the active compounds are mixed with at least one conventional inert excipient (or carrier), such as sodium citrate or dicalcium phosphate, or mixed with any of the following components: (a) fillers or compatibilizer, such as starch, lactose, sucrose, glucose, mannitol and silicic acid; (b) binders, such as
20 hydroxymethyl cellulose, alginate, gelatin, polyvinylpyrrolidone, sucrose and arabic gum; (c) humectant, such as, glycerol; (d) disintegrating agent, such as agar, calcium carbonate, potato starch or tapioca starch, alginic acid, certain composite silicates, and sodium carbonate; (e) dissolution-retarding agents, such as paraffin; (f) absorption accelerators, such as quaternary ammonium compounds; (g) wetting agents, such as cetyl alcohol and
25 glyceryl monostearate; (h) adsorbents, for example, kaolin; and (i) lubricants such as talc, stearin calcium, magnesium stearate, solid polyethylene glycol, lauryl sodium sulfate, or the mixtures thereof. In capsules, tablets and pills, the dosage forms may also contain buffering agents.

The solid dosage forms such as tablets, sugar pills, capsules, pills and granules can be
30 prepared by using coating and shell materials, such as enteric coatings and any other materials known in the art. They can contain an opaque agent. The release of the active compounds or compounds in the compositions can be released in a delayed mode in a given portion of the digestive tract. Examples of the embedding components include polymers and waxes. If necessary, the active compounds and one or more above excipients
35 can form microcapsules.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or tinctures. In addition to the active compounds, the liquid dosage forms may contain any conventional inert diluents known in the art such as water or other solvents, solubilizers and emulsifiers, such as ethanol, isopropanol, ethyl carbonate, ethyl acetate, propylene glycol, 1,3-butanediol, dimethyl formamide, as well as oil, in particular, cottonseed oil, peanut oil, corn germ oil, olive oil, castor oil and sesame oil, or the combination thereof.

Besides these inert diluents, the composition may also contain additives such as wetting agents, emulsifiers, suspending agent, sweetener, flavoring agents and perfume.

In addition to the active compounds, the suspension may contain suspending agent, for example, ethoxylated isooctadecanol, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, methanol aluminum and agar, or the combination thereof.

The compositions for parenteral injection may comprise physiologically acceptable sterile aqueous or anhydrous solutions, dispersions, suspensions or emulsions, and sterile powders which can be re-dissolved into sterile injectable solutions or dispersions. Suitable aqueous and non-aqueous carriers, diluents, solvents or excipients include water, ethanol, polyols and any suitable mixtures thereof.

The dosage forms for topical administration of compounds of the invention include ointments, powders, patches, aerosol, and inhalants. The active ingredients are mixed with physiologically acceptable carriers and any preservatives, buffers, or propellant if necessary, under sterile conditions.

Compounds of the present invention can be administrated alone, or in combination with any other pharmaceutically acceptable compounds.

When the pharmaceutical compositions are used, a safe and effective amount of compound of the present invention is administered to a mammal (such as human) in need thereof, wherein the dose of administration is a pharmaceutically effective dose. For a person weighing 60 kg, the daily dose is usually 1-2000 mg, preferably 50-1000mg. Of course, the particular dose should also depend on various factors, such as the route of administration, patient health status, which are well within the skills of an experienced physician.

The present invention also provides a preparation method of pharmaceutical composition comprising the step of mixing a pharmaceutically acceptable carrier with the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof of the present invention.

The main advantages of the present invention include:

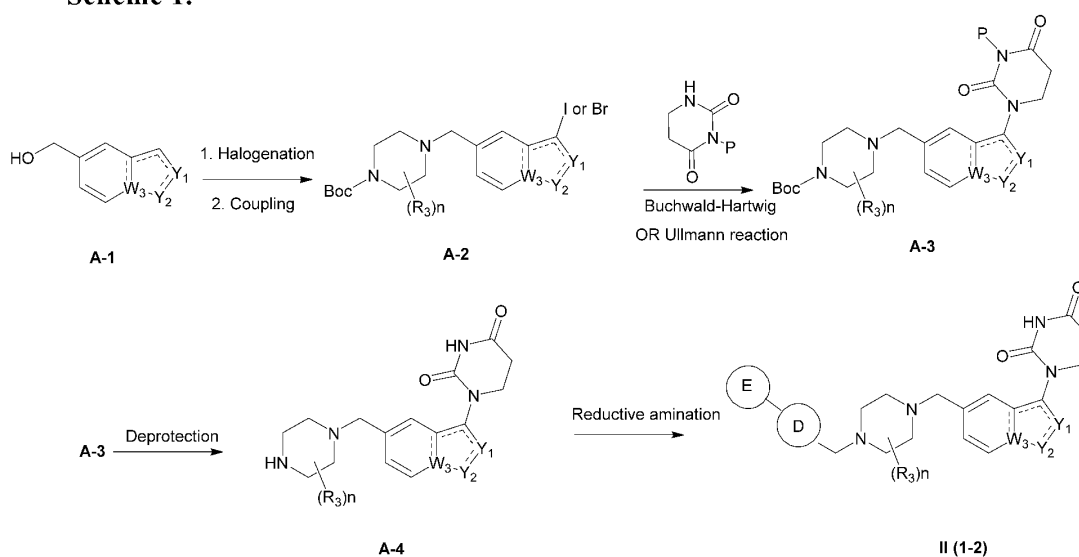
1. The compounds described in the present invention possess novel structure.
2. The compounds described in the present invention are effective to reduce or modulate widely interspaced zinc finger motifs (WIZ) protein expression levels and/or induce fetal hemoglobin (HbF) expression.
3. The compounds described in the present invention possess a low clearance rate, good oral exposure, and high oral bioavailability.

The present invention is further described below in conjunction with specific examples. It is to be understood that these examples are intended to illustrate the invention only and not to limit the scope of the invention. The following embodiments do not indicate the specific conditions of the experimental method, usually according to the conventional conditions, or according to the conditions recommended by the manufacturer. Unless otherwise specified, percentages and parts are calculated by weight.

Example**Methods of Preparing a Compound of the Invention**

Compounds of the present invention may be prepared using reactions and techniques known in the art and those described herein. One of the skills in the art will appreciate that methods of preparing compounds of the invention described herein are non-limiting and that steps within the methods may be interchangeable without affecting the structure of the end product.

Preferably, compounds described in the present invention may be prepared as shown in Scheme 1-3:

Scheme 1.

As shown in Scheme 1, compounds of formula **(II (1-2))** of the invention may be prepared using conventional organic syntheses and commercially available starting materials.

5 **General step 1:**

The starting materials of **A-1** is halogenated under the condition of NBS, or NIS or Br₂ under the solvent of ACN, DMF or DCM, then the intermediate is oxidated under the condition of MnO₂ or other oxidizing reagents. After obtaining the aldehyde intermediate, a piperazine derivative is coupling with the aldehyde in presence of NaBH(AcO)₃ with the
10 catalysis of AcOH to yield the compound **A-2**.

General step 2:

The compound **A-2** is subjected to Buchwald-Hartwig reaction to produce the compound **A-3** in presence of Pd catalysis or Ullmann reaction in presence of Cu catalysis in a solvent (such as dioxane, DMF, or DMSO). The yields of cross-coupling reactions vary
15 with different substrates and catalysts.

General step 3:

The protective groups of compound **A-3** can be removed by HCl/dioxane, TFA, or TFA and TfOH to yield the deprotected compound **A-4**.

General step 4:

20 The compound of formula **II (1-2)** can be synthesized through a reductive amination of compound **A-4** with an appropriate aldehyde or ketone in the presence of a reducing agent (for example NaBH₃CN) and AcOH. Alternatively, compound of formula **II (1-2)** can be synthesized through an alkylation reaction of compound **A-4** using an appropriate alkyl halide, mesylate, tosylate or triflate in the presence of an amine or carbonate base and
25 polar solvent, such as DIPEA or K₂CO₃ and DMF. Wherein W₃, Y₂, Y₁, rings **D** and g **E** are as defined in the claim.

Scheme 2.



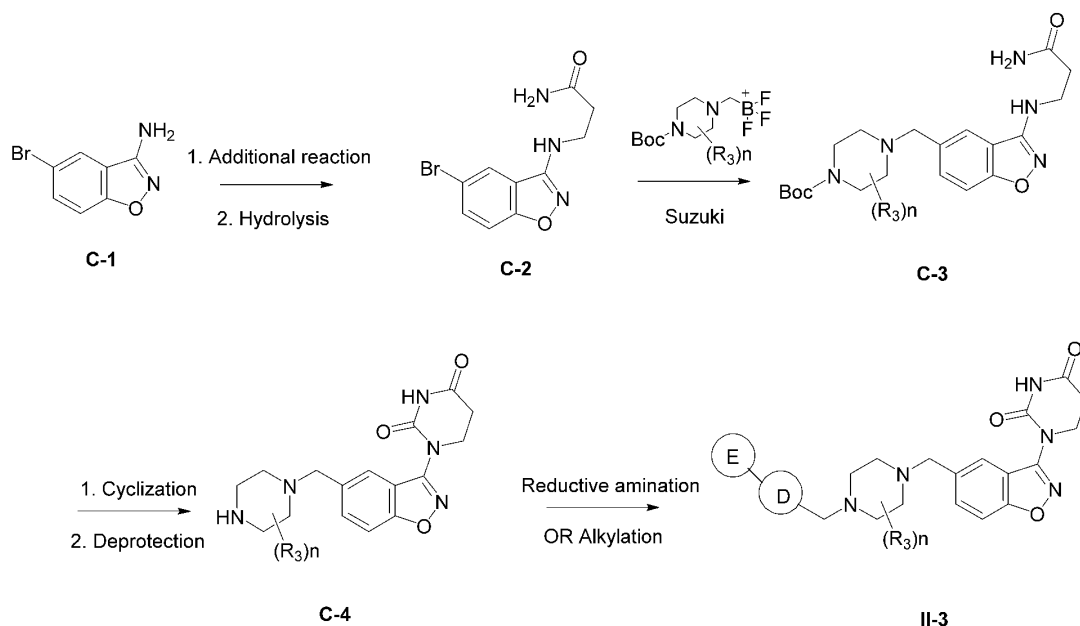
General step 5:

The second step is followed by **General step 2**.

General step 6:

General step 7:

Scheme 3.



As shown in Scheme 3, compounds of formula **II-3** of the invention may be prepared using conventional organic syntheses and commercially available starting materials.

General step 8:

- 5 The amino group of the commercially available 5-bromobenzo[d]isoxazol-3-amine reacts with acrylonitrile under base conditions (such as Cs_2CO_3). Then, the intermediate of cyano groups is hydrolyzed by H_2SO_4 to give amide **C-2**.

General step 9:

- 10 The bromo **C-2** can be substituted through Suzuki reaction. To provide the compound **C-3**, the bromo can be reacted with a boranyle derivative in presence of Pd-catalysis (such as Ruphos Pd G3), a solvent, such as DMF or dioxane, a base, such as Cs_2CO_3 .

General step 10:

- 15 The primary amide and amino groups of **C-3** are cyclized with a carbonyl equivalent to form a dihydrouracil moiety, such as 1,1'-carbonyldiimidazole (CDI) in the presence of an amine or carbonate base, such as Cs_2CO_3 , and a polar solvent, such as acetonitrile. Removal of the protective group (e.g., Boc) under acidic circumstances at room temperature can yield the free amine **C-4**.

General step 11:

- 20 **C-4** can then be converted to formula **II-3** by reductive amination with an appropriate aldehyde in the presence of a borohydride reagent, such as NaBH_3CN ; alternatively, by an alkylation reaction with an appropriate alkyl halide, mesylate, tosylate or triflate in the presence of an amine or carbonate base and polar solvent, such as DIPEA or K_2CO_3 and DMF.

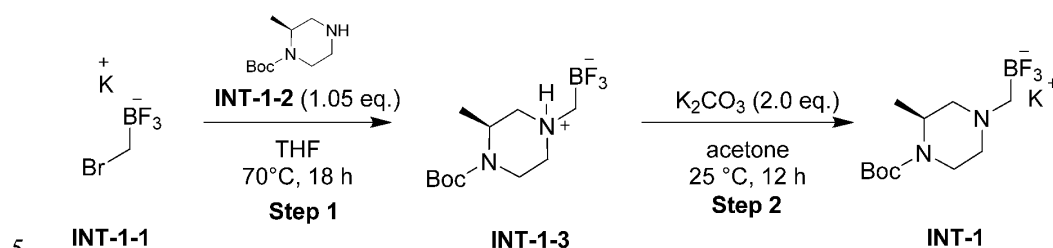
Chemistry

Several methods for preparing the compounds of the invention are illustrated hereinbelow. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Hereinafter, ACN means acetonitrile, AcOH means acetic acid, Boc means tert-butyloxycarbonyl, Bn means benzyl, BH₃ means borane, *t*-BuOK means potassium tert-butoxide, BINAP means 1,1'-binaphthyl-2,2'-diphenyl phosphine, calcd. means calculated, Cbz means benzyloxycarbonyl, col. means column, conc. means concentrated, CDI means 1,1'-carbonyldiimidazole, DCM means dichloromethane, DIEA or DIPEA means *N,N*-diisopropylethyl amine, DMF means dimethylformamide, DMP means Dess-Martin periodinane, DMSO means dimethyl sulphoxide, DPPP means 1,3-bis(diphenylphosphine)propane, Et₃N means triethylamine, EtOAc or EA means ethyl acetate, ee means enantiomeric excess, ESI means electrospray ionization, FA means formic acid, HATU means 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, Hex means hexane, HNMR means ¹H NMR, HCl means hydrochloric acid, HPLC means high performance liquid chromatography, IPA means isopropyl alcohol, LC-MS or LCMS means liquid chromatography-mass spectrometry, LDA means lithium diisopropylamide, LAH means lithium aluminum hydride, Ms means methanesulfonyl, NIS means *N*-iodosuccinimide, NBS means *N*-bromosuccinimide, NaBH₃CN means sodium cyanoborohydride, PE means petroleum ether, PMB means 4-methoxybenzyl, PPTS means pyridinium *p*-toluenesulfonate, prep. means preparative, Prep-HPLC means preparative HPLC, PCC means pyridinium chlorochromate, PdCl₂(dppf) means [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), Pd₂(dba)₃ means tris(dibenzylideneacetone)dipalladium(0), ¹R or Rt mean retention time, (s) or (s) mean solid, sat. means saturated, SFC means supercritical fluid chromatography, SOCl₂ means thionyl chloride, TBAF means tetrabutylammonium fluoride, TBS means tert-butyldimethylsilyl, TEA means triethylamine, T₃P means *n*-propylphosphonic cyclic anhydride, THF means tetrahydrofuran, TFA means trifluoroacetic acid, T or Temp mean temperature, TMS means trimethylsilyl, TsCl means 4-toluenesulfonyl chloride, Tf₂O means trifluoromethanesulfonic anhydride, TfOH means trifluoromethanesulfonic, K₂CO₃ means potassium carbonate, RuPhos Pd G3 means RuPhos-G3-Palladacycle, Methanesulfonato(2-dicyclohexylphosphino-2',6'-di-isopropoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II), W means wavelength.

Intermediates preparation

Preparation of Intermediate INT-1: Potassium (*S*)-((4-(*tert*-butoxycarbonyl)-3-methylpiperazin-1-yl)methyl)trifluoroborate



Step 1: Synthesis of (((3*S*)-4-(*tert*-butoxycarbonyl)-3-methylpiperazin-1-ium-1-yl)methyl)trifluoroborate

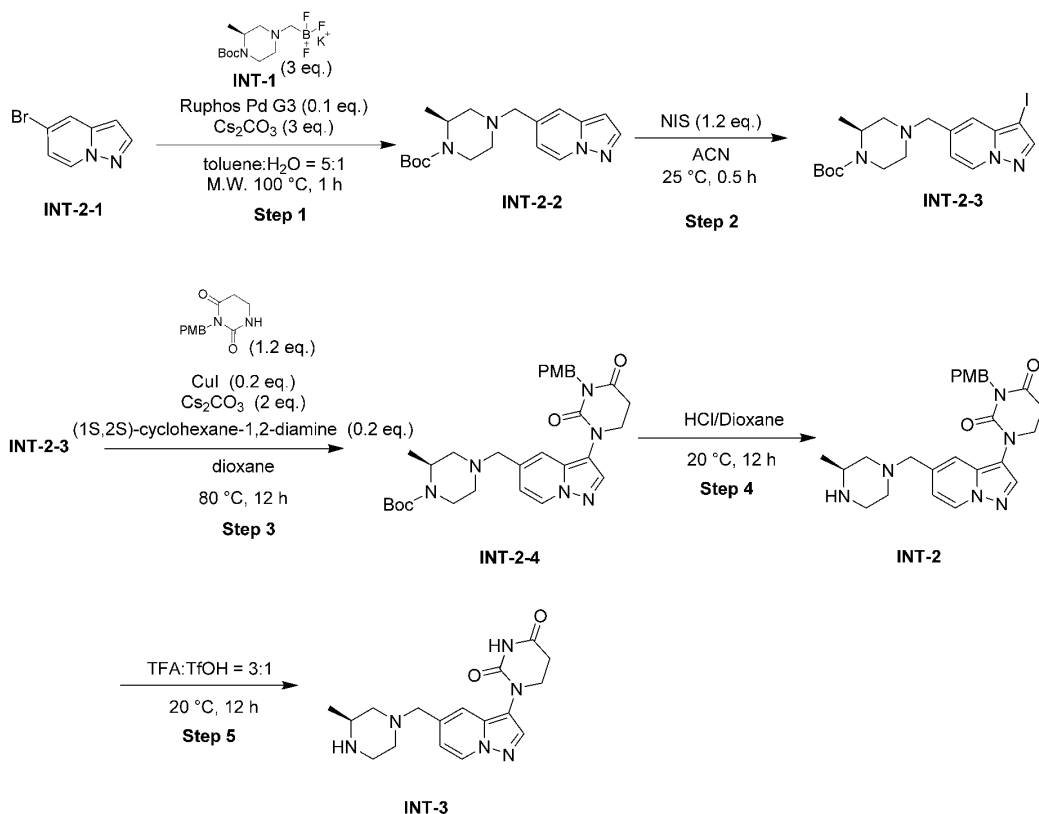
A mixture of potassium (bromomethyl)trifluoroborate (3.00 g, 14.9 mmol) and *tert*-butyl (2*S*)-2-methylpiperazine-1-carboxylate (3.14 g, 15.7 mmol) in THF (30 mL) was stirred at 70 °C for 18 hrs under nitrogen atmosphere. The mixture was concentrated under reduced pressure to afford the crude product

(((3*S*)-4-(*tert*-butoxycarbonyl)-3-methylpiperazin-1-ium-1-yl)methyl)trifluoroborate (6.14 g, crude) (white solids) which was used for the next step without further purification.

Step 2: Synthesis of potassium (*S*)-((4-(*tert*-butoxycarbonyl)-3-methylpiperazin-1-yl)methyl)trifluoroborate

To a solution of (((3*S*)-4-(*tert*-butoxycarbonyl)-3-methylpiperazin-1-ium-1-yl)methyl)trifluoroborate (6.14 g, crude) in acetone (90 mL) was added K₂CO₃ (4.13 g, 29.9 mmol). The mixture was stirred at 25 °C for 12 hrs. The mixture was filtered, the filter cake was washed with acetone (50 mL). Then the filter cake was dried to give the potassium (*S*)-((4-(*tert*-butoxycarbonyl)-3-methylpiperazin-1-yl)methyl)trifluoroborate (7.5 g, crude) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.98 - 3.86 (m, 1H), 3.57 - 3.48 (m, 1H), 2.92 - 2.83 (m, 1H), 2.79 (d, *J* = 11.6 Hz, 1H), 2.69 (d, *J* = 11.6 Hz, 1H), 1.73 - 1.66 (m, 1H), 1.56 - 1.45 (m, 1H), 1.37 (s, 9H), 1.23 - 1.14 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H).

Preparation of Intermediate INT-2 and INT-3: (*S*)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Step 1: Synthesis of *tert*-butyl (S)-2-methyl-4-(pyrazolo[1,5-*a*]pyridin-5-ylmethyl)piperazine-1-carboxylate

- 5 The mixture of 5-bromopyrazolo[1,5-*a*]pyridine (500 mg, 2.54 mmol), potassium [(3*S*)-4-*tert*-butoxycarbonyl-3-methyl-piperazin-1-yl]methyl-trifluoro-boranuide (2.44 g, 7.61 mmol), Cs₂CO₃ (2.48 g, 7.61 mmol), toluene (5 mL) and H₂O (1 mL) were added to a microwave tube before sparged with N₂ for 5 min, then treated with RuPhos Pd G3 (212 mg, 254 μmol). The mixture was sparged with N₂ for another 5 minutes and then stirred at 100 °C under microwave
- 10 irradiation for 1 h. The mixture was concentrated under reduced pressure, which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 20 mL/min). Compound *tert*-butyl (2*S*)-2-methyl-4-(pyrazolo[1,5-*a*]pyridin-5-ylmethyl)piperazine-1-carboxylate (900 mg, 75.1% yield, 70% purity) was obtained as a white solid. R_f = 0.3 (Petroleum ether: Ethyl acetate = 3: 1).
- 15 ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.42 (s, 1H), 6.84 (dd, *J* = 1.2, 7.2 Hz, 1H), 6.45 (d, *J* = 1.6 Hz, 1H), 4.20 (s, 1H), 3.83 (d, *J* = 12.8 Hz, 1H), 3.58 - 3.35 (m, 2H), 3.18 - 3.06 (m, 1H), 2.78 (d, *J* = 11.2 Hz, 1H), 2.59 (d, *J* = 12.0 Hz, 1H), 2.18 (dd, *J* = 4.0, 11.2 Hz, 1H), 2.11 - 2.01 (m, 1H), 1.46 (s, 9H), 1.25 (d, *J* = 6.8 Hz, 3H).

Step 2: Synthesis of *tert*-butyl (S)-4-((3-iodopyrazolo[1,5-*a*]pyridin-5-yl)methyl)piperazine-1-carboxylate

-2-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl (2*S*)-2-methyl-4-(pyrazolo[1,5-*a*]pyridin-5-ylmethyl)piperazine-1-carboxylate (400 mg, 1.21 mmol) in ACN (5 mL) was added NIS (327 mg, 1.45 mmol). The mixture was stirred at 25 °C for 5 30 min. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 30 mL/min). Compound *tert*-butyl (5*S*)-4-((3-iodopyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (367 mg, 66.4% yield) was obtained as a white solid. R_f = 0.6 (Petroleum ether: Ethyl acetate = 3: 1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 (d, *J* = 7.2 Hz, 1H), 8.08 (s, 1H), 7.40 (s, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 4.14 - 4.06 (m, 1H), 3.74 - 3.68 (m, 1H), 3.67 - 3.62 (m, 1H), 3.48 - 3.44 (m, 1H), 3.11 - 2.99 (m, 1H), 2.84 - 2.77 (m, 1H), 2.64 - 2.59 (m, 1H), 2.12 - 2.01 (m, 2H), 1.40 (s, 9H), 1.23 - 1.19 (m, 3H).

Step 3: Synthesis of *tert*-butyl (5*S*)-4-((3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl (5*S*)-4-((3-iodopyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (267 mg, 585 μmol) and 3-(4-methoxybenzyl)dihydropyrimidine-2, 4(1*H*, 3*H*)-dione (164 mg, 702 μmol) in dioxane (4 mL) was added CuI (22.3 mg, 117 μmol), Cs₂CO₃ (381 mg, 1.17 mmol) and (1*S*,2*S*)-cyclohexane-1,2-diamine (13.4 mg, 117 μmol). The mixture was stirred at 80 °C for 12 hrs. The mixture was concentrated under reduced pressure, which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 15 mL/min). Compound *tert*-butyl (5*S*)-4-((3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (200 mg, 60.8% yield) was obtained as a colorless oil. R_f = 0.5 (Ethyl acetate/Petroleum ether = 0: 1). ¹H NMR (400 MHz, CDCl₃) δ 8.34 (d, *J* = 7.2 Hz, 1H), 7.88 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.19 (s, 1H), 6.93 - 6.77 (m, 3H), 4.99 (s, 2H), 4.26 - 4.17 (m, 1H), 3.86 - 3.76 (m, 6H), 3.57 - 3.37 (m, 2H), 3.17 - 3.07 (m, 1H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.81 - 2.69 (m, 1H), 2.59 (d, *J* = 11.2 Hz, 1H), 2.24 - 2.07 (m, 2H), 1.46 (s, 9H), 1.28 - 1.25 (m, 3H).

Step 4: Synthesis of (5*S*)-3-(4-methoxybenzyl)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione hydrochloride

A mixture of *tert*-butyl (5*S*)-4-((3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (1.40 g, 2.49

mmol) and HCl/dioxane (4 M, 15 mL, 24.1 eq) was stirred at 20 °C for 2 hrs. The mixture was concentrated under reduced pressure. The crude product was purified by reversed-phase HPLC (Condition: 15% to 45% of phase B (Phase A: water (neutral), Phase B: MeCN, Flow rate: 30 mL/min) and directly dry-freezing. Compound (*S*)-3-(4-methoxybenzyl)-1-(5-((3-

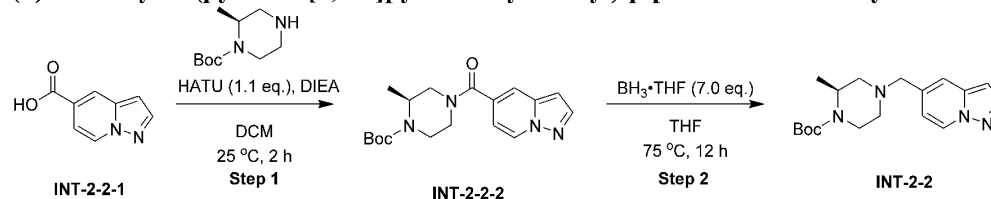
5 methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl) dihydropyrimidine-2,4(1*H*,3*H*)-dione hydrochloride (1.2 g, 2.40 mmol, HCl salt) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.61 (d, *J* = 7.2 Hz, 1H), 8.05 (s, 1H), 7.41 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.93 - 6.85 (m, 3H), 4.83 (s, 2H), 3.79 (t, *J* = 6.8 Hz, 2H), 3.74 (s, 3H), 3.56 (s, 2H), 3.24 - 3.18 (m, 2H), 3.01 - 2.93 (m, 3H), 2.89 - 2.79 (m, 2H), 2.41 - 2.30 (m, 1H), 2.19 - 2.08 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 3H).

Step 5: Synthesis of (*S*)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl) dihydropyrimidine-2,4(1*H*,3*H*)-dione

To a solution of *tert*-butyl (*S*)-4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (200 mg, 0.355 mmol) in TFA (3 mL) and TfOH (1 mL) was stirred at 25 °C for 12 hrs. The mixture was adjusted pH = 7~8 with sat. NaHCO₃ solution and concentrated in vacuo, which was purified by reversed-phase HPLC (Condition: 20% to 50% of phase B (Phase A: water (neutral), Phase B: MeCN, Flow rate: 20 mL/min) and directly dry-freezing. Compound (*S*)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl) dihydropyrimidine-2,4(1*H*,3*H*)-dione (80 mg, 65.7% yield, 70% purity) was obtained as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.47 (s, 1H), 8.60 (d, *J* = 7.2 Hz, 1H), 8.02 (s, 1H), 7.49 (s, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 3.81 - 3.71 (m, 2H), 3.56 (s, 2H), 3.21 - 3.09 (m, 2H), 2.95 - 2.75 (m, 6H), 2.37 - 2.26 (m, 1H), 2.14 - 2.05 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H).

Alternate synthetic method of INT-2-2: *tert*-butyl

25 (*S*)-2-methyl-4-(pyrazolo[1,5-*a*]pyridin-5-ylmethyl) piperazine-1-carboxylate



Step 1: Synthesis of *tert*-butyl (2*S*)-2-methyl-4-(pyrazolo[1,5-*a*]pyridine-5-carbonyl)piperazine-1-carboxylate

To a solution of pyrazolo[1,5-*a*]pyridine-5-carboxylic acid (2 g, 12.33 mmol) in DCM (30 mL) was added DIEA (3.19 g, 24.67 mmol) and HATU (5.16 g, 13.57 mmol). The mixture was stirred at 25 °C for 0.5 hr. Then *tert*-butyl (2*S*)-2-methylpiperazine-1-carboxylate (2.47 g, 12.33 mmol) was added, and the mixture was stirred at 25 °C for 1.5 hrs. The mixture was poured into

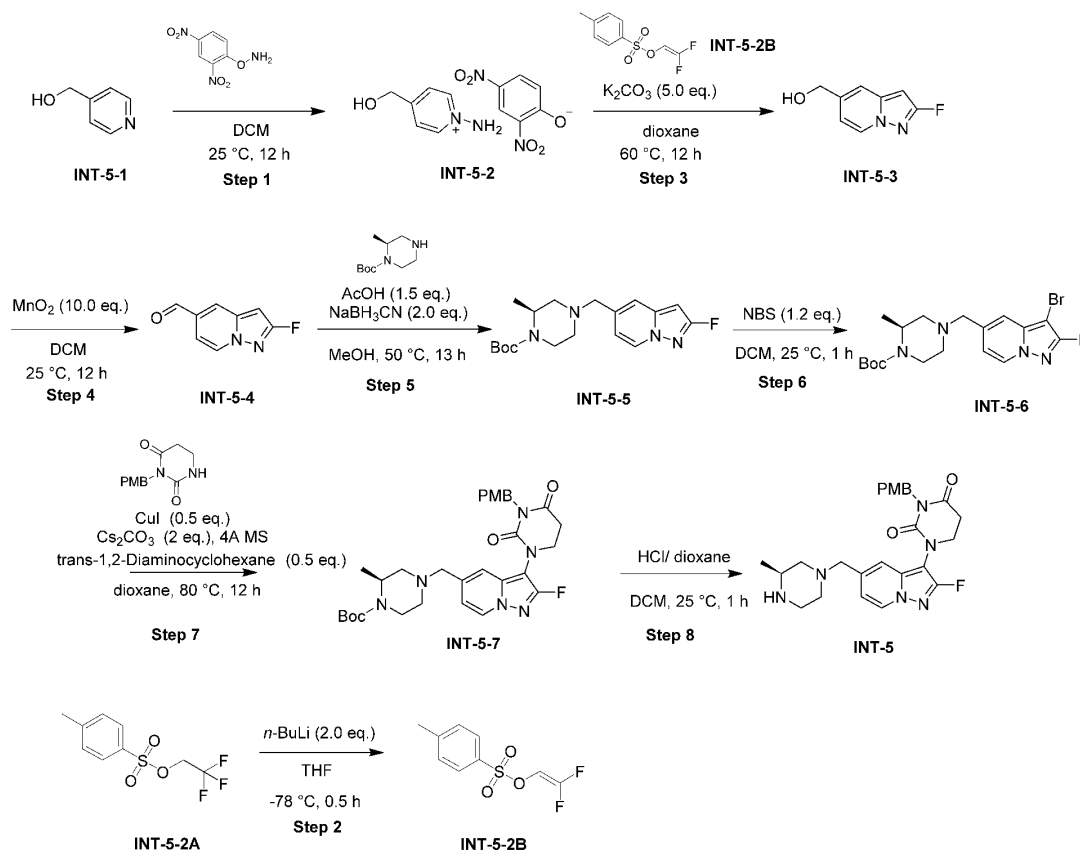
water (30 mL) and extracted with DCM (30 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ether gradient @ 40 mL/min). Compound *tert*-butyl (2*S*)-2-methyl-4-(pyrazolo[1,5-*a*]pyridine-5-carbonyl)piperazine-1-carboxylate (4.47 g, crude) was obtained as a yellow oil. R_f = 0.4 (Petroleum ether / Ethyl acetate = 1:1). ¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 2.4 Hz, 1H), 7.63 (s, 1H), 6.79 (dd, *J* = 1.2, 7.2 Hz, 1H), 6.63 (d, *J* = 1.2 Hz, 1H), 4.65 - 4.22 (m, 2H), 4.03 - 3.84 (m, 1H), 3.68 - 3.33 (m, 1H), 3.24 - 3.05 (m, 2H), 2.88 - 2.86 (m, 1H), 1.47 (s, 9H), 1.24 - 1.01 (m, 3H). LCMS (ESI+): *m/z* 345.4 [M+H]⁺.

Step 2: Synthesis of *tert*-butyl (2*S*)-2-methyl-4-(pyrazolo[1,5-*a*]pyridin-5-ylmethyl)piperazine-1-carboxylate

To a solution of *tert*-butyl (2*S*)-2-methyl-4-(pyrazolo[1,5-*a*]pyridine-5-carbonyl)piperazine-1-carboxylate (2 g, 5.81 mmol) in THF (10 mL) was added BH₃•THF (1 M, 40.65 mL) at 0°C. Then the mixture was stirred at 75 °C for 12 hrs. The reaction mixture was cooled to 0 °C, then quenched with MeOH (10 mL) dropwise under N₂. Then the mixture was heated to 60 °C for 2 hrs, then cooled to 25 °C and concentrated under reduced pressure to give a residue. The crude product was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40mL/min). Compound *tert*-butyl (2*S*)-2-methyl-4-(pyrazolo[1,5-*a*]pyridin-5-ylmethyl)piperazine-1-carboxylate (1.17 g, 61.0% yield) was obtained as a colorless oil. R_f = 0.3 (Petroleum ether / Ethyl acetate = 3:1). ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.42 (s, 1H), 6.84 (dd, *J* = 1.6, 7.2 Hz, 1H), 6.45 (d, *J* = 1.6 Hz, 1H), 4.27 - 4.15 (m, 1H), 3.87 - 3.77 (m, 1H), 3.56 - 3.48 (m, 1H), 3.43 - 3.35 (m, 1H), 3.18 - 3.07 (m, 1H), 2.82 - 2.73 (m, 1H), 2.63 - 2.56 (m, 1H), 2.21 - 2.14 (m, 1H), 2.10 - 2.05 (m, 1H), 1.46 (s, 9H), 1.25 (d, *J* = 7.2 Hz, 3H). LCMS (ESI+): *m/z* 331.5 [M+H]⁺.

Preparation of Intermediate INT-5:

(*S*)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Step 1: Synthesis of (1-aminopyridin-1-ium-4-yl)methanol;2,4-dinitrophenolate

To a solution of 4-pyridylmethanol (120 g, 1.10 mol) in DCM (1600 mL) was added O-(2,4-dinitrophenyl)hydroxylamine (219 g, 1.10 mol) at 0 °C. The mixture was stirred at 25 °C for 12 hrs. The mixture was concentrated under reduced pressure to afford the crude product, which was used into the next step without further purification. Compound (1-aminopyridin-1-ium-4-yl)methanol; 2,4-dinitrophenolate (339 g, crude) was obtained as a yellow solid.

10 Step 2: Synthesis of 2,2-difluorovinyl 4-methylbenzenesulfonate

To a solution of 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (2.50 g, 9.83 mmol) in THF (30 mL) was added dropwise *n*-BuLi (2.5 M, 19.7 mmol, 7.87 mL,) at -78 °C over 10 min. After addition, the mixture was stirred at this temperature for 30 min, and then THF (5 mL) and water (5 mL) were added dropwise at -78 °C. The reaction mixture was quenched by addition sat NH₄Cl (40 mL) at 0 °C, and then extracted with EA (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash

Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 35 mL/min). Compound 2,2-difluorovinyl 4-methylbenzenesulfonate (1.80 g, 84.7% yield) was obtained as a colorless oil. $R_f = 0.43$ (Petroleum ether: Ethyl acetate = 3:1). ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 6.08 (dd, $J = 4.0, 14.4$ Hz, 1H), 2.48 (s, 3H).

Step 3: Synthesis of (2-fluoropyrazolo[1,5-a]pyridin-5-yl)methanol

To a solution of (1-aminopyridin-1-ium-4-yl)methanol;2,4-dinitrophenolate (10 g, 32.4 mmol) in dioxane (200 mL) were added K_2CO_3 (22.4 g, 162 mmol) and 2,2-difluorovinyl 4-methylbenzenesulfonate (7.60 g, 32.4 mmol) at 0°C . The mixture was stirred at 60°C for 12 hrs.

Two batches were carried out as above with the same condition.

Combined the two batches.

The mixture was poured into water (200 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product.

The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound (2-fluoropyrazolo[1,5-a]pyridin-5-yl)methanol (3.8 g, 35.3% yield) was obtained as a yellow solid. $R_f = 0.4$ (Petroleum ether: Ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, $J = 7.2$ Hz, 1H), 7.39 (s, 1H), 6.73 (dd, $J = 1.6, 7.2$ Hz, 1H), 5.97 (d, $J = 5.6$ Hz, 1H), 4.72 (d, $J = 3.2$ Hz, 2H), 1.98 (br. s., 1H).

Step 4: Synthesis of 2-fluoropyrazolo[1,5-a]pyridine-5-carbaldehyde

To a solution of (2-fluoropyrazolo[1,5-a]pyridin-5-yl)methanol (13.8 g, 83.1 mmol) in DCM (150 mL) was added MnO_2 (75.8 g, 830 mmol). The mixture was stirred at 25°C for 12 hrs.

The mixture was filtered and concentrated under reduced pressure to afford the crude product. Compound 2-fluoropyrazolo[1,5-a]pyridine-5-carbaldehyde (12.48 g, crude) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 10.14 - 9.85 (m, 1H), 8.36 (d, $J = 7.2$ Hz, 1H), 7.96 (s, 1H), 7.29 - 7.26 (m, 1H), 6.35 (d, $J = 5.6$ Hz, 1H).

Step 5: Synthesis of tert-butyl

(S)-4-((2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of 2-fluoropyrazolo[1,5-a]pyridine-5-carbaldehyde (12.48 g, 76.0

mmol), tert-butyl (2*S*)-2-methylpiperazine-1-carboxylate (18.3 g, 91.2 mmol) in MeOH (150 mL) was added AcOH (6.85 g, 114 mmol, 6.53 mL). The mixture was stirred at 50°C for 12 hrs. Then NaBH₃CN (9.56 g, 152 mmol) was added to the mixture and stirred at 25°C for 1 hr. The mixture was concentrated under reduced pressure to afford the crude

- 5 product, which was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound *tert*-butyl (2*S*)-4-((2-fluoropyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (25.0 g, 94.4% yield) was obtained as a colorless oil. *R*_f = 0.3 (Petroleum ether / Ethyl acetate = 3:1). ¹H NMR (400 MHz, CDCl₃) δ 8.25 - 8.18 (m, 1H), 7.30 (s, 1H), 6.84 (dd, *J* = 1.6, 7.2 Hz, 1H), 5.93 (d, *J* = 5.2 Hz, 1H), 4.26 - 4.16 (m, 1H), 3.88 - 3.78 (m, 1H), 3.55 - 3.33 (m, 2H), 3.20 - 3.06 (m, 1H), 2.82 - 2.70 (m, 1H), 2.63 - 2.52 (m, 1H), 2.24 - 2.14 (m, 1H), 2.08 - 2.05 (m, 1H), 1.46 (s, 9H), 1.25 (d, *J* = 6.8 Hz, 3H).

Step 6: Synthesis of *tert*-butyl

- 15 (S)-4-((3-bromo-2-fluoropyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl

(*S*)-4-((2-fluoropyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (4.42 g, 12.7 mmol) in DCM (50 mL) was added NBS (2.71 g, 15.2 mmol). The mixture

- 20 was stirred at 25 °C for 1 hr. The mixture was diluted with DCM (20 mL) and washed with H₂O (5 mL x 2), brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product. Compound *tert*-butyl (S)-4-((3-bromo-2-fluoropyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (4.9 g, 90.4% yield) was obtained as a white solid. *R*_f = 0.5 (Petroleum ether: Ethyl acetate = 3:1). ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 7.2 Hz, 1H), 7.32 (s, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 4.33 - 4.18 (m, 1H), 3.91 - 3.81 (m, 1H), 3.61 - 3.53 (m, 1H), 3.47 - 3.39 (m, 1H), 3.21 - 3.08 (m, 1H), 2.85 - 2.73 (m, 1H), 2.65 - 2.55 (m, 1H), 2.27 - 2.18 (m, 1H), 2.16 - 2.07 (m, 1H), 1.47 (s, 9H), 1.29 - 1.26 (m, 3H).

Step 7: Synthesis of *tert*-butyl

- 30 (S)-4-((2-fluoro-3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl

(*S*)-4-((3-bromo-2-fluoropyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (4.85 g, 11.4 mmol), 3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione

(3.19 g, 13.6 mmol) in dioxane (50 mL) were added CuI (1.08 g, 5.68 mmol) and Cs₂CO₃ (7.40 g, 22.70 mmol), trans-(1*S*,2*S*)-cyclohexane-1,2-diamine (648 mg, 5.68 mmol), 4A MS (7.40 g). The mixture was stirred at 80 °C for 12 hrs. The mixture was filtered and concentrated under reduced pressure to afford the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ether gradient @ 45 mL/min). Compound *tert*-butyl (S)-4-((2-fluoro-3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (1.95 g, 29.6% yield) was obtained as a white solid. *R*_f = 0.2 (Petroleum ether: Ethyl acetate = 1:1). ¹H NMR (400 MHz, CDCl₃) δ 8.19 - 8.14 (m, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.10 (s, 1H), 6.92 (dd, *J* = 1.6, 7.2 Hz, 1H), 6.87 - 6.79 (m, 2H), 5.03 - 4.92 (m, 2H), 4.25 - 4.17 (m, 1H), 3.87 - 3.81 (m, 1H), 3.79 (s, 3H), 3.75 (t, *J* = 6.8 Hz, 2H), 3.56 - 3.50 (m, 1H), 3.40 - 3.33 (m, 1H), 3.17 - 3.06 (m, 1H), 2.93 (t, *J* = 6.7 Hz, 2H), 2.79 - 2.71 (m, 1H), 2.60 - 2.51 (m, 1H), 2.20 - 2.14 (m, 1H), 2.13 - 2.06 (m, 1H), 1.46 (s, 9H), 1.23 (d, *J* = 7.2 Hz, 3H). LCMS (ESI⁺): *m/z* 581.4 [M+H]⁺

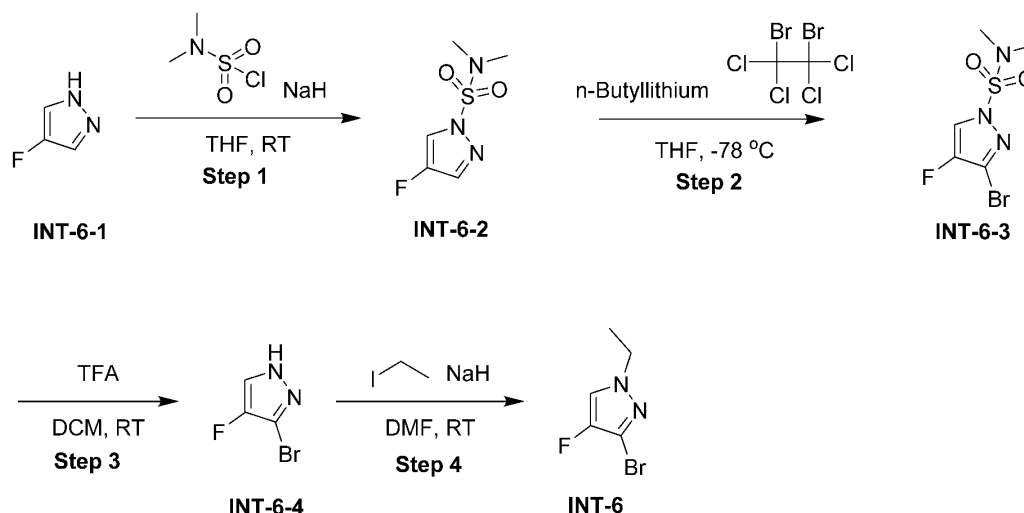
Step 8: Synthesis of

(S)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

To a solution of *tert*-butyl

(S)-4-((2-fluoro-3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (1.40 g, 2.41 mmol) in DCM (2 mL) was added HCl/dioxane (2 mL). The mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to afford the crude product. Compound (S)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.25 g, crude, HCl) was obtained as a yellow solid. The crude product was used into the next step without further purification. LCMS (ESI⁺): *m/z* 481.3 [M+H]⁺.

Preparation of Intermediate INT-6: 3-bromo-1-ethyl-4-fluoro-1*H*-pyrazole



Step 1: Synthesis of 4-fluoro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (INT-6-2)

A solution of 4-fluoro-1H-pyrazole (2.0 g, 23.2 mmol) in 20 mL THF was cooled to 0 °C, sodium hydride (828 mg, 34.8 mmol) was added. The mixture was stirred at 0 °C for 30 min, then dimethylsulfamoyl chloride (4.3 g, 34.8 mmol, dissolved in 10 mL THF) was added. The reaction mixture was stirred at the room temperature for 2 hrs. The reaction was quenched with H₂O (100 mL), extracted with EA (50 mLx2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~15% Petroleum ether/Ethyl acetate @45 ml/min). Compound 4-fluoro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (4.0 g, 88% yield) was obtained as a white solid. LCMS (ESI⁺): m/z 194.2 [M+H]⁺.

Step 2: Synthesis of 3-bromo-4-fluoro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (INT-6-3)

A solution of 4-fluoro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (4.0 g, 21 mmol) in 50 mL THF was cooled to -78 °C. *n*-Butyllithium (2.5N, 9.2 mL, 23 mmol) was added dropwise. The mixture was stirred at -78 °C for 1 hr. Then 1,2-dibromo-1,1,2,2-tetrachloroethane (7.5 g, 23 mmol, dissolved in 30 mL THF) was added. The reaction mixture was stirred at -78 °C for 2 hrs. The reaction was quenched with saturated aq. NH₄Cl (100 mL), extracted with EA (50 mLx2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 50 g SepaFlash® Silica Flash Column, Eluent of 0~15% Petroleum ether/Ethyl

acetate @60 ml/min). Compound

3-bromo-4-fluoro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (5.0 g, 89% yield) was obtained as a white solid. LCMS (ESI⁺): m/z 272.1 [M+H]⁺.

Step 3: Synthesis of 3-bromo-4-fluoro-1H-pyrazole (INT-6-4)

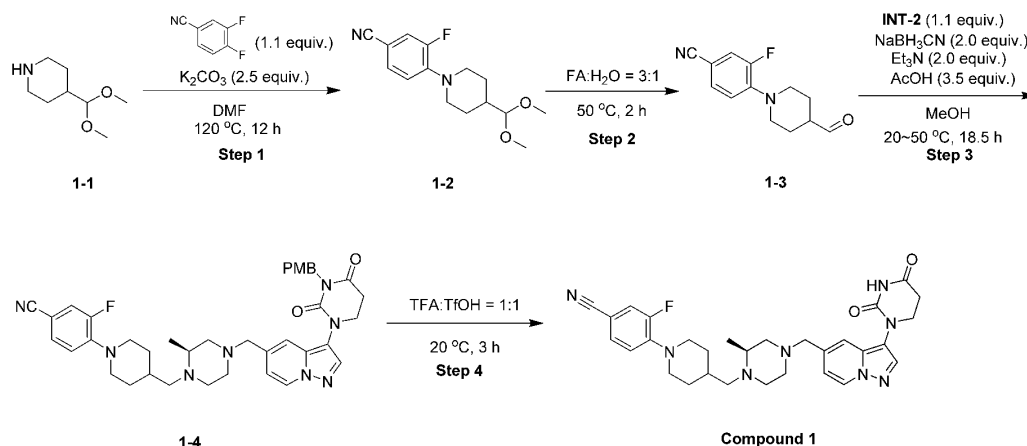
5 A mixture of 3-bromo-4-fluoro-N,N-dimethyl-1H-pyrazole-1-sulfonamide (620 mg, 2.3 mmol) and TFA (1 mL) in DCM (5 mL) was stirred for 1 hr at 50 °C. The reaction was quenched with saturated aq. NaHCO₃ (20 mL), extracted with EA (15 mLx2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure give a white solid (330 mg, 88% yield), which was
10 used into the next step without further purification. LCMS (ESI⁺): m/z 165.1 [M+H]⁺.

Step 4: Synthesis of 3-bromo-1-ethyl-4-fluoro-1H-pyrazole (INT-6)

To a solution of 3-bromo-4-fluoro-1H-pyrazole (1.5 g, 9.0 mmol) in 20 mL THF was added sodium hydride (540 mg, 13.5 mmol) at 0 °C, The mixture was stirred at 0 °C for 30 min. Then iodoethane (2.1 g, 13.5 mmol, dissolved in 10 mL THF) was added. The
15 reaction mixture was stirred for 2 hrs at the room temperature. The reaction was quenched with H₂O (100 mL), extracted with EA (50 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~15% Petroleum ether/Ethyl acetate @40
20 ml/min). Compound 3-bromo-1-ethyl-4-fluoro-1H-pyrazole (1.4 g, 78% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 193.1 [M+H]⁺.

Example 1: Preparation of compound 1:

(S)-4-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)
25 pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)-3-fluorobenzonitrile



Step 1: Synthesis of 4-(4-(dimethoxymethyl)piperidin-1-yl)-3-fluorobenzonitrile

To a solution of 4-(dimethoxymethyl)piperidine (500 mg, 3.14 mmol) in DMF (10 mL) were added K_2CO_3 (1.08 g, 7.85 mmol) and 3,4-difluorobenzonitrile (480 mg, 3.45 mmol). The mixture was stirred at 120 °C for 12 hrs. The mixture was concentrated under reduced pressure to afford the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 35mL/min) to give 4-(4-(dimethoxymethyl)piperidin-1-yl)-3-fluorobenzonitrile (700 mg, 80.1% yield) as a white solid. $R_f = 0.5$ (Ethyl acetate/Petroleum ether = 5: 1). 1H NMR (400 MHz, $DMSO-d_6$) δ 7.71 - 7.64 (m, 1H), 7.57 - 7.52 (m, 1H), 7.12 (t, $J = 8.8$ Hz, 1H), 4.10 (d, $J = 6.4$ Hz, 1H), 3.56 (d, $J = 12.4$ Hz, 2H), 3.27 (s, 6H), 2.76 (t, $J = 12.4$ Hz, 2H), 1.74 - 1.69 (m, 2H), 1.42 - 1.34 (m, 2H), 1.15 - 1.09 (m, 1H).

Step 2: Synthesis of 3-fluoro-4-(4-formyl-1-piperidyl)benzonitrile

To a solution of 4-(4-(dimethoxymethyl)piperidin-1-yl)-3-fluorobenzonitrile (100 mg, 359 μ mol, 1 eq) in H_2O (0.3 mL) was added FA (1 mL). The mixture was stirred at 50 °C for 2 hrs. The mixture was concentrated under reduced pressure to give 3-fluoro-4-(4-formyl-1-piperidyl)benzonitrile (80 mg, crude) as a light yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.29 (d, $J = 2.0$ Hz, 1H), 6.93 (t, $J = 8.8$ Hz, 1H), 3.54 (m, 2H), 3.03 - 2.87 (m, 2H), 2.54 - 2.38 (m, 1H), 2.13 - 2.00 (m, 2H), 1.91 - 1.78 (m, 2H).

Step 3: Synthesis of (S)-3-fluoro-4-(4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)benzonitrile

To a solution of (S)-3-(4-methoxybenzyl)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (94.5 mg, 189 μ mol, HCl salt) in MeOH (2 mL) was added TEA (34.9 mg, 344 μ mol) and the mixture was

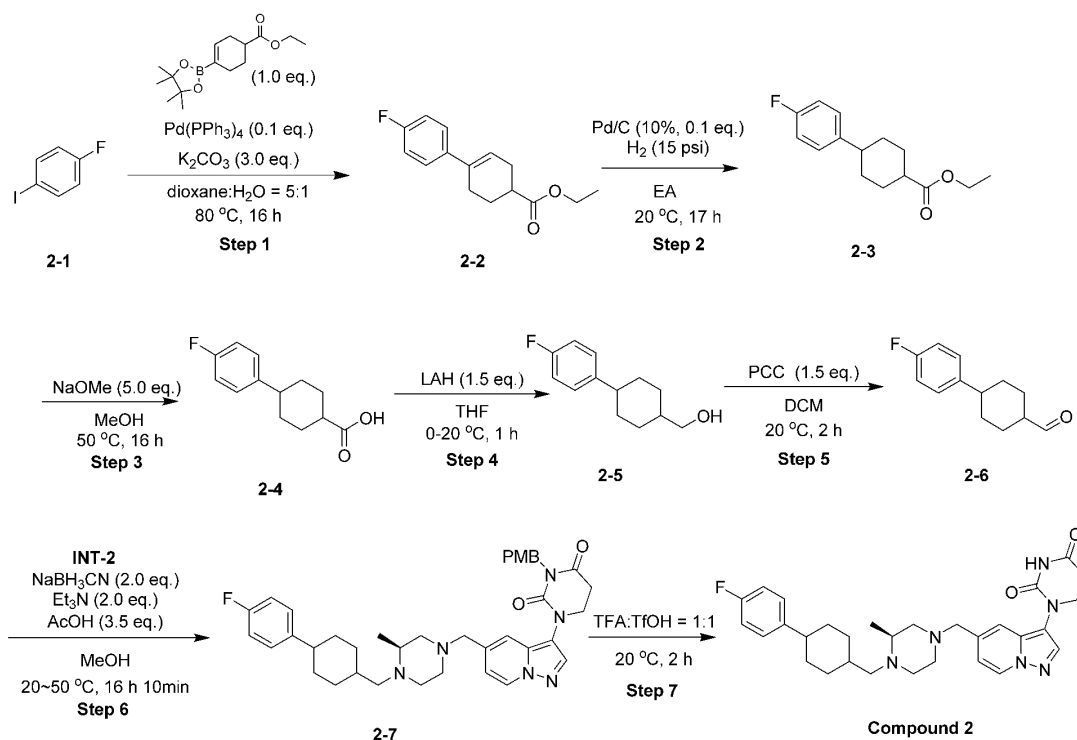
stirred at 20 °C for 30 min. Then 3-fluoro-4-(4-formyl-1-piperidyl)benzonitrile (40.0 mg, 172 µmol) and AcOH (36.2 mg, 603 µmol) were added. The mixture was stirred at 50 °C for 16 hrs. The reaction mixture was cooled to 20 °C, and NaBH₃CN (21.7 mg, 344 µmol) was added. The mixture was stirred at 20 °C for 2 hrs. The mixture was concentrated under reduced pressure.

- 5 The residue was purified by prep-TLC (DCM: MeOH = 10: 1) to give (S)-3-fluoro-4-(4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)benzonitrile (40 mg, 15.7% yield, 46% purity) as a light yellow oil. R_f = 0.66 (DCM/MeOH = 10: 1). LCMS (ESI⁺): m/z 679.6 [M+H]⁺.

10 **Step 4: Synthesis of compound 1: (S)-4-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)-3-fluorobenzonitrile**

- To a solution of (S)-3-fluoro-4-(4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)benzonitrile (40.0 mg, 58.9 µmol) in TFA (0.5 mL) was added
15 TfOH (0.5 mL). The mixture was stirred at 20 °C for 3 hrs. The mixture was adjusted pH = 7~8 with aq. NaHCO₃ solution. The resulting mixture was diluted with ethyl acetate (15 mL) and washed with water (15 mL). After partition, the aqueous layer was extracted with ethyl acetate (15 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and
20 concentrated in vacuo. The crude product was purified by reversed-phase HPLC (Condition: 40% to 60% of phase B (Phase A: water (neutral), Phase B: MeCN, Flow rate: 20 mL/min) to give (S)-4-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)-3-fluorobenzonitrile (4.38 mg, 7.74 µmol, 13.13% yield, 98.708% purity) as a white solid. ¹H NMR (400 MHz,
25 DMSO-*d*₆) δ 10.47 (s, 1H), 8.58 (d, *J* = 7.2 Hz, 1H), 8.01 (s, 1H), 7.67 (d, *J* = 13.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.11 (t, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 3.77 (t, *J* = 6.8 Hz, 2H), 3.43 - 3.42 (m, 2H), 2.81 - 2.75 (m, 5H), 2.59 - 2.56 (m, 1H), 2.48 - 2.30 (m, 2H), 2.27 - 2.13 (m, 2H), 2.03 - 1.83 (m, 4H), 1.74 - 1.62 (m, 2H), 1.36 - 1.09 (m, 4H), 0.98 - 0.93 (m, 3H), LCMS (ESI⁺): m/z 559.2 [M+H]⁺.

- 30 **Example 2: Preparation of compound 2: (S)-1-(5-((4-((4-(4-fluorophenyl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**



Step 1: Synthesis of ethyl 4-(4-fluorophenyl)cyclohex-3-ene-1-carboxylate

To a solution of 1-fluoro-4-iodobenzene (1 g, 4.50 mmol) and ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (1.26 g, 4.50 mmol) in dioxane (10 mL) and H₂O (2 mL) were added $\text{Pd}(\text{PPh}_3)_4$ (521 mg, 450 μmol) and K_2CO_3 (1.87 g, 13.5 mmol). The mixture was stirred at 80 °C for 16 hrs under N₂ atmosphere. The mixture was diluted with ethyl acetate (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethylacetate/Petroleum ether gradient @ 25 mL/min) to give ethyl 4-(4-fluorophenyl)cyclohex-3-ene-1-carboxylate (790 mg, 70.6% yield) as a yellow oil. $R_f = 0.55$ (Petroleum ether: Ethyl acetate = 10: 1). ^1H NMR (400 MHz, CDCl_3) δ 7.36 - 7.28 (m, 2H), 6.99 (t, $J = 8.8$ Hz, 2H), 6.04 (m, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 2.66 - 2.56 (m, 1H), 2.55 - 2.38 (m, 4H), 2.24 - 2.14 (m, 1H), 1.91 - 1.76 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H).

Step 2: Synthesis of ethyl 4-(4-fluorophenyl)cyclohexane-1-carboxylate

To a solution of ethyl 4-(4-fluorophenyl)cyclohex-3-ene-1-carboxylate (790 mg, 3.18 mmol) in ethyl acetate (10 mL) was added wet Pd/C (339 mg, 318 μmol , 10% w/w). The mixture was stirred at 20 °C for 17 hrs under H₂ atmosphere (15 psi). The mixture was filtered through a pad of celite and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of

0~10% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give ethyl

4-(4-fluorophenyl)cyclohexane-1-carboxylate (680 mg, 85.4% yield) as a colorless oil. R_f = 0.47 (Petroleum ether: Ethyl acetate = 10: 1). ^1H NMR (400 MHz, CDCl_3) δ 7.19 - 7.10 (m, 2H), 7.02 - 6.91 (m, 2H), 4.23 - 4.11 (m, 2H), 2.69 (s, 1H), 2.59 - 2.44 (m, 1H), 2.31 - 2.18 (m, 2H), 2.10 (d, J = 11.2 Hz, 1H), 2.02 - 1.91 (m, 1H), 1.82 - 1.71 (m, 2H), 1.64 (d, J = 8.8 Hz, 2H), 1.33 - 1.26 (m, 3H).

Step 3: Synthesis of 4-(4-fluorophenyl)cyclohexane-1-carboxylic acid

To a solution of ethyl 4-(4-fluorophenyl)cyclohexanecarboxylate (680 mg, 2.72 mmol) in MeOH (5 mL) was added NaOMe (5.4 M, 2.52 mL). The mixture was stirred at 50 °C for 16 hrs. The mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with water (10 mL) and adjusted pH = 4~5 with 1 N HCl aqueous solution. The resulting mixture was diluted with ethyl acetate (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give 4-(4-fluorophenyl)cyclohexanecarboxylic acid (650 mg, crude) was obtained as a yellow solid.

Step 4: Synthesis of (4-(4-fluorophenyl)cyclohexyl)methanol

To a solution of 4-(4-fluorophenyl)cyclohexanecarboxylic acid (650 mg, 2.92 mmol) in THF (6 mL), LiAlH_4 (1 M, 4.39 mL) was added dropwise at 0 °C under N_2 atmosphere. The mixture was stirred at 20 °C for 1 hr. The mixture was quenched by addition H_2O (200 μL) at 0 °C. Then the resulting mixture was added aq. potassium sodium tartrate solution (10 mL) and the mixture was stirred for 30 min. The mixture was diluted with ethyl acetate (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in vacuo to give (4-(4-fluorophenyl)cyclohexyl)methanol (400 mg, crude) was obtained as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 7.20 - 7.12 (m, 2H), 6.97 (t, J = 8.8 Hz, 2H), 3.52 (d, J = 6.0 Hz, 2H), 2.55 - 2.42 (m, 1H), 1.95-1.91 (m, 4H), 1.57 - 1.38 (m, 4H), 1.19 - 1.06 (m, 2H).

Step 5: Synthesis of 4-(4-fluorophenyl)cyclohexanecarbaldehyde

To a solution of (4-(4-fluorophenyl)cyclohexyl)methanol (130 mg, 624.19 μmol) in DCM (2 mL) was added PCC (201.82 mg, 936.28 μmol). The mixture was stirred at 20 °C for 2 hrs. The mixture was filtered through a pad of Celite® and concentrated in vacuo to give 4-(4-fluorophenyl)cyclohexanecarbaldehyde (100 mg, crude) as a light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 9.68 (s, 1H), 7.19 - 7.13 (m, 2H), 7.04 - 6.95 (m, 2H), 2.55 - 2.44 (m, 1H), 2.35 - 2.26 (m, 1H), 2.15-2.10 (m, 2H), 2.03 - 2.00 (m, 2H), 1.50 - 1.40 (m, 4H).

Step 6: Synthesis of (S)-1-(5-((4-((4-fluorophenyl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

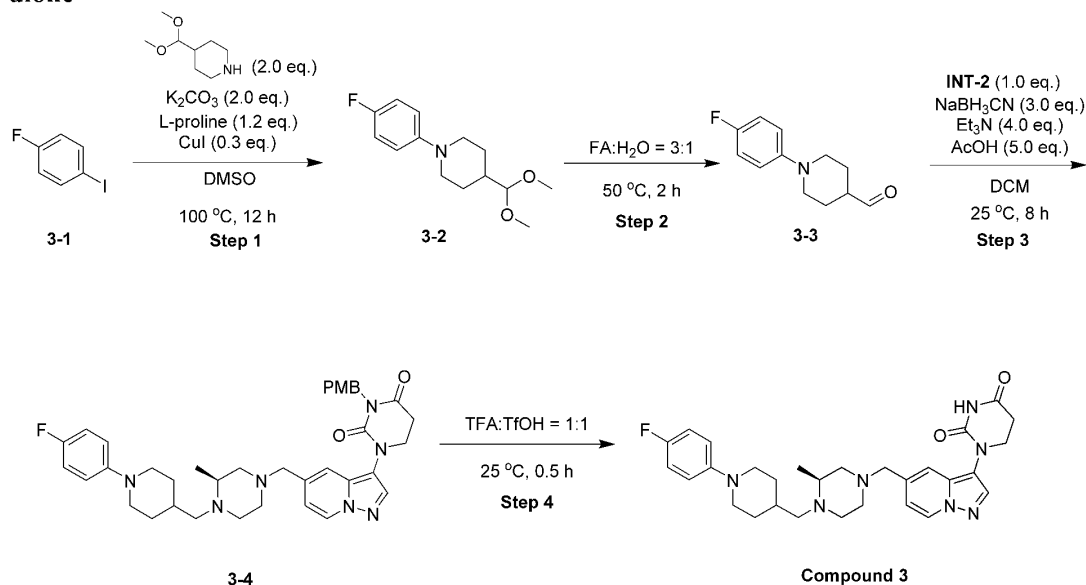
To a solution of (S)-3-(4-methoxybenzyl)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione hydrochloride (70.0 mg, 140.3 μmol , HCl salt) in MeOH (2 mL) was added TEA (28.4 mg, 281 μmol) and the mixture was stirred at 20 $^{\circ}\text{C}$ for 10 min. Then 4-(4-fluorophenyl)cyclohexanecarbaldehyde (57.9 mg, 281 μmol) and AcOH (29.5 mg, 491 μmol) were added. The mixture was stirred at 50 $^{\circ}\text{C}$ for 2 hrs. The reaction mixture was cooled to 20 $^{\circ}\text{C}$, and NaBH_3CN (17.6 mg, 280.6 μmol) was added. The mixture was stirred at 20 $^{\circ}\text{C}$ for 14 hrs. The mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM: MeOH = 15: 1) to give (S)-1-(5-((4-((4-fluorophenyl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (40 mg, 30.1% yield, 69% purity) as a yellow oil. R_f = 0.43 (DCM/MeOH = 15: 1). LCMS (ESI^+): m/z 653.6 $[\text{M}+\text{H}]^+$.

Step 7: Synthesis of compound 2: (S)-1-(5-((4-((4-fluorophenyl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

To a solution of (S)-1-(5-((4-((4-fluorophenyl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (40.0 mg, 61.27 μmol) in TFA (0.5 mL) was added TfOH (0.5 mL, 5.65 mmol). The mixture was stirred at 20 $^{\circ}\text{C}$ for 2 hrs. The mixture was adjusted pH=7~8 with sat. NaHCO_3 solution. The resulting mixture was diluted with ethyl acetate (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by prep-HPLC (Column: Kromasil 100-5-C18 30*150 mm, mobile phase A: water (0.01% FA), mobile phase B: acetonitrile, 25 mL/min, gradient condition from 10% B to 40%) to give (S)-1-(5-((4-((4-fluorophenyl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (1.8 mg, 5.08% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.45 (br. s, 1H), 8.58 (d, J = 7.2 Hz, 1H), 8.01 (s, 1H), 7.45 (s, 1H), 7.32 - 7.18 (m, 2H), 7.15 - 7.01 (m, 2H), 6.94 - 6.83 (m, 1H), 3.85 - 3.69 (m, 2H), 3.46 - 3.45 (m, 2H), 2.86 - 2.73 (m, 4H), 2.70 - 2.65 (m, 1H), 2.42 - 2.30 (m, 2H), 2.28 - 2.18 (m, 2H), 2.04 - 1.91 (m, 3H), 1.84 - 1.70 (m, 3H), 1.58 - 1.33 (m, 4H), 1.06 - 0.87 (m, 5H), LCMS (ESI^+): m/z 533.4 $[\text{M}+\text{H}]^+$.

Example 3: Preparation of compound 3:

(S)-1-(5-(((4-((1-(4-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione



5

3-4

Compound 3

Step 1: Synthesis of 4-(dimethoxymethyl)-1-(4-fluorophenyl)piperidine

The reaction mixture of 1-fluoro-4-iodo-benzene (1.00 g, 4.50 mmol), 4-(dimethoxymethyl)piperidine (1.43 g, 9.01 mmol), K_2CO_3 (1.25 g, 9.01 mmol), L-proline (622 mg, 5.41 mmol) in DMSO (20 mL) was purged with nitrogen stream for 3 min, followed by addition of CuI (257 mg, 1.35 mmol). The resulting mixture was heated at 100 °C for 12 hrs. The mixture was added saturated aq. $NaHCO_3$ to adjust pH 6-7, then extracted with ethyl acetate (30 mL x 2). The combined organic extracts were washed with brine (30 mL x 3), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product.

The crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 30mL/min) to give 4-(dimethoxymethyl)-1-(4-fluorophenyl)piperidine (550 mg, 48.2% yield) as a colorless oil. R_f = 0.69 (Ethyl acetate/Petroleum ether = 5: 1). 1H NMR (400MHz, $CDCl_3$) δ 7.01 - 6.86 (m, 4H), 4.13 - 4.07 (m, 1H), 3.57 (d, J = 12.0 Hz, 2H), 3.38 (s, 6H), 2.62 (t, J = 11.6 Hz, 2H), 1.90 - 1.82 (m, 2H), 1.77 - 1.67 (m, 1H), 1.53 - 1.43 (m, 2H).

Step 2: Synthesis of 1-(4-fluorophenyl)piperidine-4-carbaldehyde

4-(dimethoxymethyl)-1-(4-fluorophenyl)piperidine (0.1 g, 394.77 μ mol) was added to a mixture of HCOOH (0.75 mL) and H₂O (0.25 mL), and the mixture was stirred at 50 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give

1-(4-fluorophenyl)piperidine-4-carbaldehyde (90 mg, crude, FA) as a yellow oil. LCMS (ESI⁺): m/z 208.2 [M+H]⁺.

Step 3: Synthesis of (S)-1-(5-((4-((1-(4-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1*H*,3*H*)-dione

To a solution of 1-(4-fluorophenyl)piperidine-4-carbaldehyde (71.06 mg, 280.56 μ mol, 2 *eq*, FA), (S)-3-(4-methoxybenzyl)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridine-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione hydrochloride (70.0 mg, 140 μ mol, HCl) in DCM (2 mL) was added TEA (56.8 mg, 561 μ mol) to adjust pH 7~8. The mixture was stirred for 0.5 hr, then AcOH (42.1 mg, 701 μ mol) was added, and stirred at 25 °C for 5.5 hrs. Then NaBH₃CN (26.5 mg, 421 μ mol) was added into the mixture and stirred at 25 °C for 2 hrs. The mixture was concentrated under reduced pressure to afford the crude product. The crude product was purified by prep-TLC (DCM/MeOH=10/1) to give (S)-1-(5-((4-((1-(4-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (88.0 mg, crude) as a yellow oil. LCMS (ESI⁺): m/z 654.6 [M+H]⁺.

Step 4: Synthesis of compound 3: (S)-1-(5-((4-((1-(4-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1*H*,3*H*)-dione

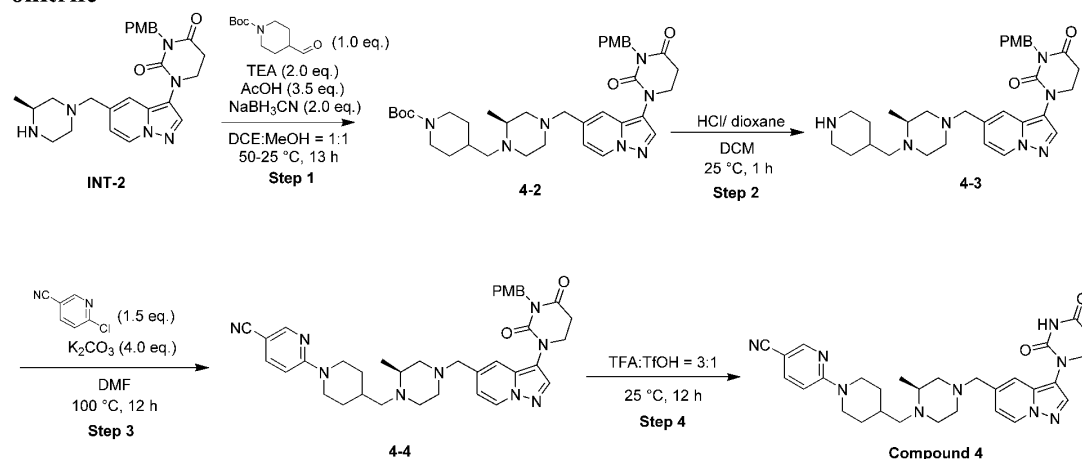
(S)-1-(5-((4-((1-(4-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (88.0 mg, 135 μ mol) was added into a mixture of TFA (0.5 mL) and TfOH (0.5 mL). The mixture was stirred at 25 °C for 0.5 hr. The mixture was adjusted pH=7~8 with saturated aq. NaHCO₃ solution. The resulting mixture was diluted with ethyl acetate (5 mL) and washed with water (3 mL). After partition, the aqueous layer was extracted with ethyl acetate (5 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (Column: Kromasil 100-5-C18 30*150 mm, mobile phase A: water (0.01% FA), mobile phase B: acetonitrile, 25 mL/min, gradient condition from 1% B to 40%) to give (S)-1-(5-((4-((1-(4-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (15.0 mg, 20.9% yield) as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 10.47 (br. s, 1H), 8.58 (d, *J* = 6.8 Hz, 1H), 8.01 (s, 1H), 7.51 - 7.38 (m, 1H), 7.05 - 6.98 (m, 2H), 6.96 - 6.86 (m, 3H), 3.86 - 3.68 (m, 2H), 3.53 - 3.51 (m, 2H), 2.85 - 2.72 (m, 5H), 2.69 - 2.66 (m, 1H), 2.37 - 2.31 (m, 2H), 2.26 - 2.09 (m, 4H), 1.99 - 1.81 (m, 4H), 1.74 - 1.49 (m, 2H), 1.29 - 1.06 (m, 2H), 0.95 (d, *J* = 5.6 Hz, 3H), LCMS

(ESI⁺): m/z 534.2 [M+H]⁺.

Example 4: preparation of compound 4:

(*S*)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)

5 pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile



Step 1: Synthesis of *tert*-butyl (*S*)-4-((4-((3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate

(*S*)-3-(4-methoxybenzyl)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (585 mg, 1.17 mmol, HCl) in DCE (4 mL) and MeOH (4 mL) was added TEA (237 mg, 2.34 mmol). The mixture was stirred at 25 °C for 5 min. Then the mixture were added *tert*-butyl 4-formylpiperidine-1-carboxylate (250 mg, 1.17 mmol) and AcOH (246 mg, 4.10 mmol). The mixture was stirred at 50 °C for 12 hrs. Then the mixture was added NaBH₃CN (147 mg, 2.34 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 hr. The mixture was poured into water (10 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol/Dichloromethane gradient @ 20 mL/min). Compound *tert*-butyl (*S*)-4-((4-((3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (400 mg, 51.7% yield) was obtained as a white solid. R_f = 0.43 (Dichloromethane: Methanol = 10: 1). ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.24 (s, 1H), 6.89 - 6.77 (m, 3H), 4.21 - 4.06 (m, 2H), 3.80 - 3.77 (m, 3H), 3.59 - 3.53 (m, 2H), 3.51 - 3.46 (m, 4H), 3.15 - 3.06 (m, 5H), 3.00 - 2.94 (m, 2H), 2.83 - 2.76 (m, 3H), 2.72 - 2.68 (m, 1H), 2.40 - 2.33 (m,

2H), 1.93 - 1.77 (m, 3H), 1.72 - 1.66 (m, 1H), 1.45 (s, 9H), 1.26 - 1.16 (m, 4H).

Step 2: Synthesis of (S)-3-(4-methoxybenzyl)-1-(5-((3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

5 To a solution of *tert*-butyl (S)-4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (400 mg, 606 μ mol) in DCM (3 mL) and HCl/dioxane (3 mL) was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure, which was used into the next step without further purification. Compound (S)-3-(4-methoxybenzyl)-
10 1-(5-((3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (360 mg, HCl, crude) was obtained as a white solid. LCMS (ESI⁺): m/z 560.4 [M+H]⁺.

Step 3: Synthesis of (S)-6-(4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile

15 To a solution of (S)-3-(4-methoxybenzyl)-1-(5-((3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (50 mg, 83.9 μ mol, HCl) and 6-chloropyridine-3-carbonitrile (17.4 mg, 126 μ mol) in DMF (1 mL) was added K₂CO₃ (46.4 mg, 335 μ mol). The mixture was stirred at 100 °C for 12 hrs. The mixture
20 was concentrated under reduced pressure, which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol/Dichloromethane gradient @ 20 mL/min). Compound (S)-6-(4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile (29.0 mg,
25 40.2% yield) was obtained as a colorless oil. R_f = 0.4 (Dichloromethane: Methanol = 10: 1) LCMS (ESI⁺): m/z 662.4 [M+H]⁺.

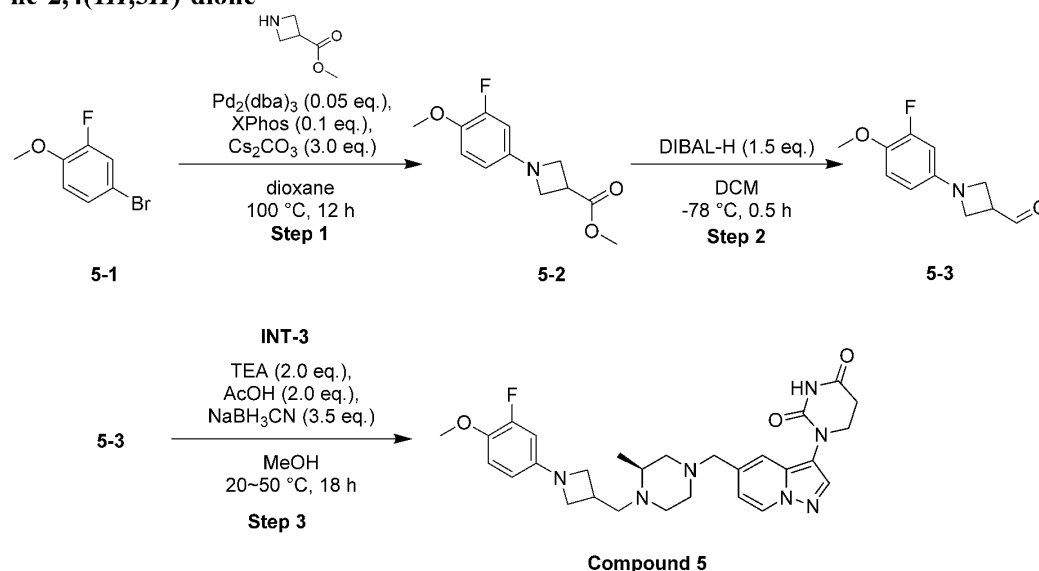
Step 4: Synthesis of compound 4: (S)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile

30 To a solution of (S)-6-(4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile (29.0 mg, 43.8 μ mol) in a mixture of TFA (1 mL) and TfOH (1 mL) was stirred at 25 °C for 12 hrs. The mixture was adjusted pH=7~8 with saturated aq. NaHCO₃ solution and extracted with EtOAc (5 mL x 3). The organic layer was washed with brine (5 mL), dried over
35 anhydrous Na₂SO₄, filtered and concentrated under reduced pressure, which was purified by

reversed-phase HPLC (Condition: 10% to 50% of phase B (Phase A: water (FA), Phase B: MeCN, Flow rate: 20 mL/min) and directly dry-freezing. Compound (*S*)-6-4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile (5.17 mg, 21.8% yield) was obtained as a white solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 10.44 (br. s., 1H), 8.57 (d, *J* = 7.2 Hz, 1H), 8.44 (d, *J* = 2.4 Hz, 1H), 8.01 (s, 1H), 7.79 (dd, *J* = 2.4, 9.2 Hz, 1H), 7.44 (s, 1H), 6.94 - 6.85 (m, 2H), 4.47 - 4.33 (m, 2H), 3.79 - 3.75 (m, 2H), 3.01 - 2.85 (m, 3H), 2.82 - 2.75 (m, 3H), 2.70 - 2.52 (m, 3H), 2.48 - 2.43 (m, 1H), 2.37 - 2.30 (m, 1H), 2.25 - 2.14 (m, 2H), 1.99 - 1.90 (m, 2H), 1.88 - 1.76 (m, 2H), 1.72 - 1.63 (m, 1H), 1.11 - 0.96 (m, 2H), 0.93 (d, *J* = 6.2 Hz, 3H). LCMS (ESI⁺): *m/z* 542.3 [M+H]⁺.

Example 5: Preparation of compound 5:

(*S*)-1-(5-((4-((1-(3-fluoro-4-methoxyphenyl)azetidine-3-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



Step 1: Synthesis of methyl 1-(3-fluoro-4-methoxyphenyl)azetidine-3-carboxylate

A mixture of 4-bromo-2-fluoro-1-methoxybenzene (1.00 g, 4.88 mmol), methyl azetidine-3-carboxylate (739 mg, 4.88 mmol, HCl salt), XPhos (233 mg, 488 μmol) and Cs_2CO_3 (4.77 g, 14.6 mmol) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then $\text{Pd}_2(\text{dba})_3$ (223.32 mg, 243.87 μmol) was added to the mixture and stirred at 100 °C for 12 hr under N_2 atmosphere. H_2O (20 mL) was added to the mixture and extracted with DCM (30 mL x 3). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate: Petroleum ether @ 100 mL/min). Compound

methyl 1-(3-fluoro-4-methoxy-phenyl)azetidine-3-carboxylate (700 mg, 60.0% yield) was obtained as a yellow oil. $R_f = 0.3$ (Petroleum ether/ Ethyl acetate=4: 1). LCMS (ESI+): m/z 241.2 $[M+H]^+$

Step 2: Synthesis of 1-(3-fluoro-4-methoxyphenyl)azetidine-3-carbaldehyde

Diisobutylaluminum (1.5 M, 1.25 mL, 1.88 mmol) was added in a dropwise manner to a solution of methyl 1-(3-fluoro-4-methoxy-phenyl)azetidine-3-carboxylate (300 mg, 1.25 mmol) in DCM (15 mL) at -78 °C. The mixture was stirred at -78 °C for 0.5 hr. The mixture was quenched with 50% aqueous rochelle salt aqueous solution (10 mL) at 0 °C. The mixture was stirred at 25 °C for 3 hrs. The mixture was poured into water (10 mL) and extracted with DCM (20 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product, which was used in the next step without further purification. Compound 1-(3-fluoro-4-methoxy-phenyl)azetidine-3-carbaldehyde (260 mg, 99.1% yield) was obtained as a colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 9.94 (d, $J = 2.4$ Hz, 1H), 6.95 - 6.79 (m, 1H), 6.32 - 6.23 (m, 1H), 6.20 - 6.14 (m, 1H), 4.04 - 3.95 (m, 4H), 3.83 (s, 3H), 3.48 - 3.44 (m, 1H).

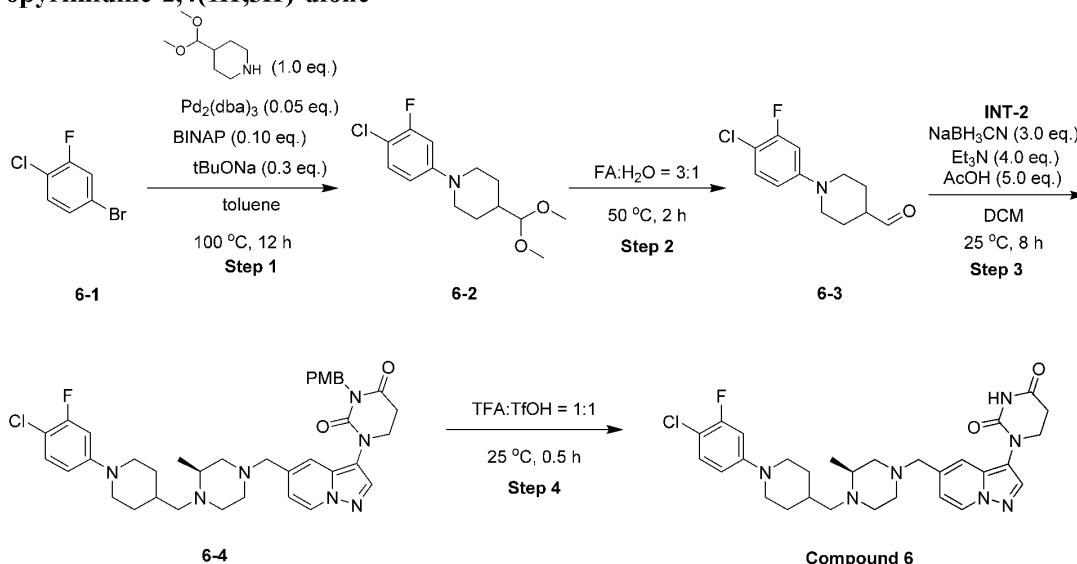
Step 3: Synthesis of compound 5: (S)-1-(5-((4-((1-(3-fluoro-4-methoxyphenyl)azetidin-3-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

To a solution of (S)-1-(5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (16.37 mg, 47.80 μ mol) in MeOH (3 mL) was added TEA (9.67 mg, 95.59 μ mol, 13.31 μ L) and the mixture was stirred at 20 °C for 10 min. Then 1-(3-fluoro-4-methoxy-phenyl)azetidine-3-carbaldehyde (10 mg, 47.80 μ mol) and AcOH (5.74 mg, 95.59 μ mol) were added. The mixture was stirred at 50 °C for 16 hrs. The reaction mixture was cooled to 20 °C, and $NaBH_3CN$ (10.51 mg, 167.29 μ mol) was added. The mixture was stirred at 20 °C for 2 hrs. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: Kromasil 100-5-C18 30*150 mm, mobile phase A: water (0.01% TFA), mobile phase B: acetonitrile, 25 mL/min, gradient condition from 30% B to 70%). The pure fractions were lyophilized to give a compound, which was redissolved in a solution consisting of ACN (5 mL) and HCl (0.5%, 5 mL) and lyophilized to give the desired product. Compound (S)-1-(5-((4-((1-(3-fluoro-4-methoxyphenyl)azetidin-3-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (4.62 mg, 16.90% yield, HCl salt) was obtained as a white solid.

1H NMR (400 MHz, $DMSO-d_6$) δ 10.53 (br. s., 1H), 8.74 (d, $J = 6.8$ Hz, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.27 (d, $J = 5.6$ Hz, 1H), 7.10 - 6.93 (m, 1H), 6.52 - 6.38 (m, 1H), 6.36 - 6.22 (m, 1H), 4.53 - 4.33 (m, 2H), 4.04 - 3.96 (m, 2H), 3.84 - 3.78 (m, 4H), 3.75 - 3.71 (m, 9H), 3.35 - 3.29 (m,

1H), 3.27 - 3.19 (m, 1H), 2.89 - 2.76 (m, 2H), 2.63 - 2.54 (m, 1H), 2.49 - 2.40 (m, 1H), 1.45 - 1.33 (m, 3H). LCMS (ESI+): m/z 536.2 $[M+H]^+$.

Example 6: Preparation of compound 6: (S)-1-(5-((4-((1-(4-chloro-3-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydr
opyrimidine-2,4(1H,3H)-dione



Step 1: Synthesis of 1-(4-chloro-3-fluorophenyl)-4-(dimethoxymethyl)piperidine

To a solution of 4-bromo-1-chloro-2-fluorobenzene (395 mg, 1.88 mmol) in toluene (5 mL) was added 4-(dimethoxymethyl)piperidine (300 mg, 1.88 mmol), BINAP (117 mg, 188 μ mol), $Pd_2(dba)_3$ (86.27 mg, 94.21 μ mol) and t-BuONa (543 mg, 5.65 mmol). The mixture was stirred at 100 °C for 12 hrs under N_2 . The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethylacetate/Petroleum ether gradient @ 30 mL/min). Compound 1-(4-chloro-3-fluoro-phenyl)-4-(dimethoxymethyl)piperidine (400 mg, 73.8% yield) was obtained as a yellow oil. R_f = 0.5 (Petroleum ether: Ethyl acetate = 5: 1). 1H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, J = 8.8 Hz, 1H), 6.71 - 6.60 (m, 2H), 4.07 (d, J = 7.2 Hz, 1H), 3.71 - 3.62 (m, 2H), 3.37 (s, 6H), 2.73 - 2.63 (m, 2H), 1.87 - 1.80 (m, 2H), 1.58 (s, 1H), 1.44 - 1.36 (m, 2H).

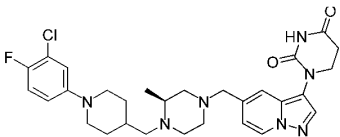
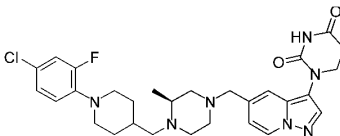
Step 2~4: Synthesis of compound 6: (S)-1-(5-((4-((1-(4-chloro-3-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydr
opyrimidine-2,4(1H,3H)-dione

Prepared from 1-(4-chloro-3-fluorophenyl)-4-(dimethoxymethyl)piperidine by following the synthesis procedure of compound 3.

Compound (*S*)-1-(5-(((4-((1-(4-chloro-3-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (8.09 mg, 49.0% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.44 (br. s., 1H), 8.56 (d, *J* = 7.2 Hz, 1H), 8.00 (s, 1H), 7.43 (s, 1H), 7.33 - 7.24 (m, 1H), 6.94 - 6.85 (m, 2H), 6.77 - 6.71 (m, 1H), 3.78 - 3.68 (m, 4H), 2.77 (t, *J* = 6.4 Hz, 3H), 2.71 - 2.53 (m, 5H), 2.47 - 2.43 (m, 1H), 2.38 - 2.32 (m, 1H), 2.25 - 2.12 (m, 2H), 1.98 - 1.89 (m, 2H), 1.85 - 1.78 (m, 1H), 1.69 - 1.60 (m, 2H), 1.27 - 0.99 (m, 3H), 0.93 (d, *J* = 6.0 Hz, 3H). LCMS (ESI⁺): *m/z* 568.3 [M+H]⁺.

10 **Example 7:** The following compounds in **Table 1** were prepared by the method of **compound 4**

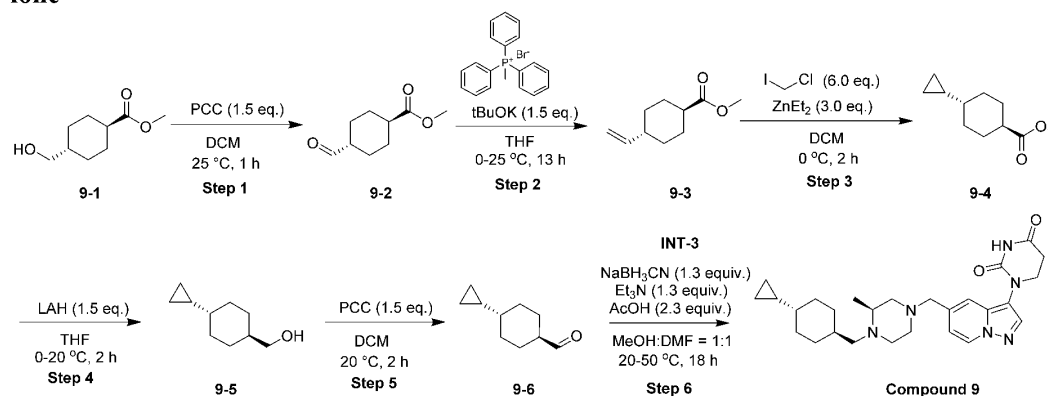
Table 1

No.	Structure	Compound name and characterization
7		(<i>S</i>)-1-(5-(((4-((1-(3-chloro-4-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5- <i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.44 (s, 1H), 8.58 (d, <i>J</i> = 7.2 Hz, 1H), 8.01 (s, 1H), 7.45 (s, 1H), 7.24 - 7.17 (m, 1H), 7.03 (dd, <i>J</i> = 3.2, 6.4 Hz, 1H), 6.94 - 6.86 (m, 2H), 3.77 (t, <i>J</i> = 6.8 Hz, 2H), 3.68 - 3.47 (m, 2H), 2.81 - 2.75 (m, 3H), 2.67 - 2.57 (m, 8H), 2.29 - 2.21 (m, 2H), 2.09 - 1.96 (m, 2H), 1.87 - 1.80 (m, 1H), 1.75 - 1.53 (m, 2H), 1.26 - 1.07 (m, 2H), 0.97 (d, <i>J</i> = 6.0 Hz, 3H); LCMS (ESI ⁺): <i>m/z</i> 568.3 [M+H] ⁺ , Retention time: 2.25 min;
8		(<i>S</i>)-1-(5-(((4-((1-(4-chloro-2-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5- <i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.44 (br. s, 1H), 8.57 (d, <i>J</i> = 7.2 Hz, 1H), 8.00 (s, 1H), 7.43 (s, 1H), 7.29 (dd, <i>J</i> = 1.6, 12.4 Hz, 1H), 7.17 - 7.12 (m, 1H), 7.05 - 6.99 (m, 1H), 6.88 (d, <i>J</i> = 7.6 Hz, 1H), 3.76 (t, <i>J</i> = 6.8 Hz, 2H), 3.50 - 3.49 (m, 2H), 2.77 (t, <i>J</i> = 6.8 Hz, 3H), 2.68 - 2.55 (m, 5H), 2.36 - 2.32 (m, 1H), 2.25 - 2.12 (m, 3H), 1.99 - 1.91 (m, 2H), 1.89 - 1.79 (m, 1H), 1.73 - 1.65 (m, 1H), 1.61 - 1.52 (m, 1H), 1.33 - 1.14 (m, 3H), 0.95 (d, <i>J</i> = 5.6

		Hz, 3H); LCMS (ESI ⁺): m/z 568.4 [M+H] ⁺ , Retention time: 2.70 min;
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Example 8: Preparation of compound 9:**1-(5-(((S)-4-(((1R,4S)-4-cyclopropylcyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

5

**Step 1: Synthesis of methyl (1R,4R)-4-formylcyclohexane-1-carboxylate**

To a solution of methyl methyl (1R,4R)-4-(hydroxymethyl)cyclohexane-1-carboxylate (500 mg, 2.90 mmol) in DCM (5 mL) was added PCC (938.7 mg, 4.35 mmol). The mixture was stirred at 25 °C for 1 hr. The mixture was filtered and concentrated under reduced pressure to afford the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethylacetate/Petroleum ether gradient @40 mL/min) to give methyl methyl (1R,4R)-4-formylcyclohexane-1-carboxylate (380 mg, 76.9% yield) as a white solid. R_f = 0.5 (Petroleum ether: Ethyl acetate = 4: 1). ¹H NMR (400 MHz, CDCl₃) δ 9.64 (s, 1H), 3.68 (s, 3H), 2.34 - 2.20 (m, 2H), 2.16 - 2.02 (m, 4H), 1.57 - 1.42 (m, 2H), 1.38 - 1.23 (m, 2H).

Step 2: Synthesis of methyl (1R,4R)-4-vinylcyclohexane-1-carboxylate

To a solution of methyltriphenylphosphonium bromide (6.30 g, 17.6 mmol) in THF (30 mL) was added *t*-BuOK (1 M, 17.6 mL) at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 1 hr. Then a solution of (1R,4R)-4-formylcyclohexane-1-carboxylate (2 g, 11.7 mmol) in THF (20 mL) was added slowly. The reaction was warmed to 20 °C and stirred for 12 hrs. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with EtOAc (20 mL X 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give

methyl (1*R*,4*R*)-4-vinylcyclohexane-1-carboxylate (660 mg, 33.4% yield) as a colorless liquid. $R_f = 0.6$ (Petroleum ether: Ethyl acetate = 4: 1). ^1H NMR (400 MHz, CDCl_3) δ 5.82 - 5.70 (m, 1H), 5.02 - 4.88 (m, 2H), 3.69 - 3.64 (m, 3H), 2.31 - 2.20 (m, 1H), 2.05 - 1.91 (m, 3H), 1.91 - 1.79 (m, 2H), 1.52 - 1.41 (m, 2H), 1.19 - 1.05 (m, 2H).

5 **Step 3: Synthesis of methyl (1*R*,4*R*)-4-cyclopropylcyclohexane-1-carboxylate**

To a solution of methyl (1*R*,4*R*)-4-vinylcyclohexane-1-carboxylate (600.0 mg, 3.57 mmol) in DCM (15 mL), ZnEt_2 (1 M, 10.7 mL) was added dropwise at 0 °C under N_2 atmosphere. Then chloriodomethane (3.77 g, 21.40 mmol, 1.55 mL) was added dropwise. The mixture was stirred at 0 °C for 2 hrs. The reaction was quenched by addition saturated aq. NH_4Cl (15 mL).

10 The resulting mixture was diluted with DCM (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with DCM (20 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give methyl (1*R*,4*R*)-4-cyclopropylcyclohexane-1-carboxylate (610 mg, crude) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 3.68 - 3.62 (m, 3H), 2.30 - 2.19 (m, 1H), 2.01 - 1.94 (m, 2H),
15 1.93 - 1.84 (m, 2H), 1.41 - 1.28 (m, 2H), 1.17 - 1.03 (m, 2H), 0.51 - 0.41 (m, 2H), 0.40 - 0.34 (m, 2H), 0.08 - 0.01 (m, 2H).

Step 4: Synthesis of methyl ((1*R*,4*R*)-4-cyclopropylcyclohexyl)methanol

To a solution of methyl (1*R*,4*R*)-4-cyclopropylcyclohexane-1-carboxylate (610 mg, 3.35 mmol) in THF (8 mL), LiAlH_4 (1 M, 5.02 mL) was added dropwise at 0 °C under N_2
20 atmosphere. The mixture was stirred at 20 °C for 2 hrs. The mixture was quenched by addition aq. $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ solution (10 mL) and the mixture was stirred for 30 min. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in vacuo to give ((1*R*,4*R*)-4-cyclopropylcyclohexyl)methanol (420 mg,
25 crude) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 3.46 - 3.41 (m, 2H), 1.89 - 1.77 (m, 4H), 1.55 - 1.51 (m, 1H), 1.16 - 1.03 (m, 2H), 0.93 - 0.82 (m, 2H), 0.51 - 0.33 (m, 4H), 0.08 - 0.01 (m, 2H)

Step 5: Synthesis of (1*R*,4*R*)-4-cyclopropylcyclohexane-1-carbaldehyde

To a solution of ((1*R*,4*R*)-4-cyclopropylcyclohexyl)methanol (75 mg, 486.2 μmol) in DCM (2
30 mL) was added PCC (157.2 mg, 729.3 μmol). The mixture was stirred at 20 °C for 2 hrs. The mixture was filtrated through a pad of celite and concentrated in vacuo to give (1*R*,4*R*)-4-cyclopropylcyclohexane-1-carbaldehyde (50 mg, crude) as a light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 9.61 (s, 1H), 2.25 - 2.13 (m, 1H), 2.04 - 1.90 (m, 4H), 1.31 - 1.07 (m, 5H), 0.50 - 0.42 (m, 1H), 0.41 - 0.33 (m, 2H), 0.09 - 0.02 (m, 2H).

Step 6: Synthesis of compound 9: 1-(5-(((S)-4-(((1R,4S)-4-cyclopropylcyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

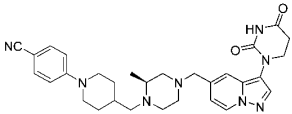
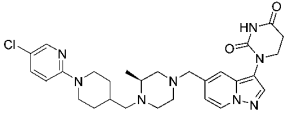
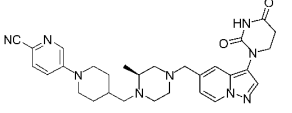
To a solution of (S)-1-(5-(((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridine-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (30 mg, 79.2 μ mol, HCl) in MeOH (0.5 mL) and DMF (0.5 mL) was added TEA (16.03 mg, 158.4 μ mol, 22.04 μ L) and the mixture was stirred at 20 °C for 10 min. Then (1R,4R)-4-cyclopropylcyclohexane-1-carbaldehyde (18.1 mg, 118.78 μ mol) and AcOH (16.6 mg, 277.2 μ mol, 15.9 μ L) were added. The mixture was stirred at 50 °C for 2 hrs. The reaction mixture was cooled to 20 °C, and NaBH₃CN (9.95 mg, 158.4 μ mol) was added. The mixture was stirred at 20 °C for 16 hrs. The mixture was concentrated under reduced pressure. The crude product was purified by reversed-phase HPLC (Condition: 40% to 70% of phase B (Phase A: water (neutral), Phase B: MeCN, Flow rate: 20 mL/min) and directly dry-freezing. Then the crude product was again purified by prep-TLC to give 1-(5-(((S)-4-(((1R,4S)-4-cyclopropylcyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (2.96 mg, 7.8% yield, 100% purity) as a white solid. R_f = 0.45 (Dichloromethane: Methanol = 10: 1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.50 (s, 1H), 8.61 (d, *J* = 7.2 Hz, 1H), 8.05 (s, 1H), 7.48 (s, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 3.80 (t, *J* = 6.8 Hz, 2H), 3.61 (s, 2H), 2.83 - 2.80 (m, 2H), 2.22 - 2.11 (m, 2H), 2.00 - 1.86 (m, 4H), 1.84 - 1.74 (m, 3H), 1.71 - 1.64 (m, 1H), 1.56 - 1.41 (m, 3H), 1.25 - 1.19 (m, 1H), 1.17 - 1.03 (m, 3H), 1.01 - 0.92 (m, 3H), 0.92 - 0.86 (m, 1H), 0.52 - 0.45 (m, 2H), 0.39 - 0.34 (m, 2H), 0.08 - 0.04 (m, 2H).

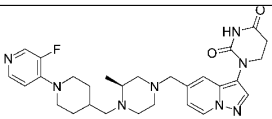
Example 9: The following compounds in **Table 2** were prepared by the method of **compound 6**

25

Table 2

No.	Structure	Compound name and characterization
10		(S)-1-(5-(((1-(5-fluoropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione. ¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 8.50 (d, <i>J</i> = 16 Hz, 1H), 7.97 (d, dd, <i>J</i> = 3.2 Hz, 1H), 7.52 (s, 1H), 7.41 - 7.36 (m, 1H), 7.03 (d, <i>J</i> = 1.6 Hz, 1H), 6.85 (d, <i>J</i> = 4 Hz, 1H), 4.62 (t, 2H), 4.22 (d, <i>J</i> = 16 Hz, 2H), 3.92 (t, 2H), 3.65 (t, 2H), 2.92 - 2.79 (m, 9H), 2.5 (m, 2H), 2.29 - 2.21 (m, 2H), 1.95-1.77(m, 2H), 1.33 - 1.27 (m, 3H), 1.20 (d, <i>J</i> = 8.0 Hz,

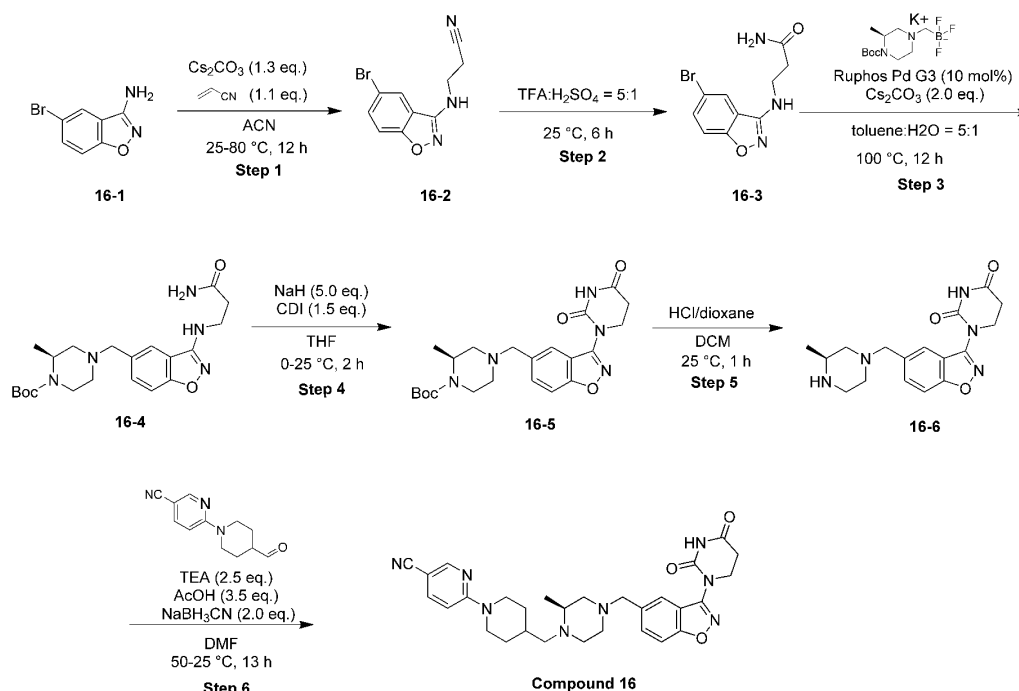
		3H); LCMS (ESI ⁺): m/z 535.44 [M+H] ⁺ .
11		(S)-4-(4-(((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)benzonitrile. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.47 (s, 1H), 8.58 (d, <i>J</i> = 8 Hz, 1H), 8.01 (s, 1H), 7.54 (d, <i>J</i> = 12 Hz, 2H), 7.45 (s, 1H), 7.00 (d, <i>J</i> = 12 Hz, 2H), 6.88 (d, <i>J</i> = 8 Hz, 1H), 3.93 (t, <i>J</i> = 4 Hz, 2H), 3.77 (m, 2H), 3.43 - 3.42 (m, 2H), 2.81 - 2.75 (m, 5H), 2.59 - 2.56 (m, 1H), 2.48 - 2.30 (m, 2H), 2.27 - 2.13 (m, 2H), 2.03 - 1.83 (m, 4H), 1.74 - 1.62 (m, 2H), 1.36 - 1.09 (m, 4H), 0.98 - 0.93 (m, 3H), LCMS (ESI⁺): m/z 541.6 [M+H]⁺.
13		(S)-1-(5-(((4-((1-(5-chloropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.47 (s, 1H), 8.58 (d, <i>J</i> = 8 Hz, 1H), 8.07 (s, 1H), 8.01 (s, 1H), 7.54 (d, <i>J</i> = 4 Hz, 1H), 7.44 (s, 1H), 6.90 (d, <i>J</i> = 4 Hz, 1H), 6.84 (d, <i>J</i> = 12 Hz, 1H), 4.22 (m, 2H), 3.77 (t, <i>J</i> = 8 Hz, 2H), 3.43 - 3.42 (m, 2H), 2.81 - 2.75 (m, 5H), 2.59 - 2.56 (m, 2H), 2.48 - 2.30 (m, 1H), 2.27 - 2.13 (m, 2H), 2.03 - 1.83 (m, 4H), 1.74 - 1.62 (m, 2H), 1.36 - 1.09 (m, 3H), 0.98 - 0.93 (m, 3H), LCMS (ESI⁺): m/z 551.42 [M+H]⁺.
14		(S)-5-(4-(((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)picolinonitrile. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.45 (br. s., 1H), 8.57 (d, <i>J</i> = 7.2 Hz, 1H), 8.39 (d, <i>J</i> = 2.8 Hz, 1H), 8.04 - 7.98 (m, 1H), 7.70 (d, <i>J</i> = 8.8 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.33 (dd, <i>J</i> = 2.8, 8.8 Hz, 1H), 6.89 (dd, <i>J</i> = 1.2, 7.2 Hz, 1H), 4.04 - 3.94 (m, 2H), 3.77 (t, <i>J</i> = 6.8 Hz, 2H), 3.48 - 3.45 (m, 2H), 3.28 - 3.26 (m, 1H), 2.96 - 2.85 (m, 2H), 2.82 - 2.75 (m, 3H), 2.64 - 2.54 (m, 2H), 2.37 - 2.31 (m, 1H), 2.24 - 2.15 (m, 2H), 1.98 - 1.89 (m, 2H), 1.88 - 1.84 (m, 1H), 1.77 - 1.65 (m, 2H), 1.16 - 1.02 (m, 2H), 0.93 (d,

		$J = 6.4 \text{ Hz, 3H}$; LCMS (ESI ⁺): m/z 542.3 [M+H] ⁺ , Retention time: 1.30 min;
15		(S)-1-(5-((4-((1-(3-fluoropyridin-4-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.44 (br. s., 1H), 8.57 (d, $J = 6.8 \text{ Hz}$, 1H), 8.21 (d, $J = 6.0 \text{ Hz}$, 1H), 8.10 (d, $J = 5.6 \text{ Hz}$, 1H), 8.01 - 8.03 (m, 1H), 7.44 - 7.46 (m, 1H), 6.94 (dd, $J = 5.6, 8.4 \text{ Hz}$, 1H), 6.88 (dd, $J = 1.6, 7.2 \text{ Hz}$, 1H), 3.77 (t, $J = 6.8 \text{ Hz}$, 2H), 3.71 - 3.62 (m, 2H), 3.47 - 3.40 (m, 2H), 3.33 - 3.30 (m, 1H), 2.87 - 2.74 (m, 5H), 2.65 - 2.55 (m, 2H), 2.39 - 2.31 (m, 1H), 2.24 - 2.11 (m, 2H), 2.00 - 1.90 (m, 2H), 1.88 - 1.81 (m, 1H), 1.73 - 1.62 (m, 2H), 1.27 - 1.09 (m, 2H), 0.94 (d, $J = 6.0 \text{ Hz}$, 3H); LCMS (ESI⁺): m/z 535.2 [M+H]⁺, Retention time: 2.64 min;

Example 10: Preparation of compound 16:

(S)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile

5



Step 1: Synthesis of 3-((5-bromobenzo[d]isoxazol-3-yl)amino)propanenitrile

To a solution of 5-bromo-1,2-benzoxazol-3-amine (10.0 g, 46.9 mmol) in ACN (100 mL) were added prop-2-enenitrile (2.07 g, 39.0 mmol) and Cs_2CO_3 (19.9 g, 61.0 mmol) at 25 °C. The mixture was stirred at 80 °C for 12 hrs. The mixture was diluted with ethyl acetate (50 mL) and washed with water (100 mL). After partition, the aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in vacuo, which was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~50% EA: PE gradient @ 100 mL/min). Compound 3-((5-bromobenzo[d]isoxazol-3-yl)amino)propanenitrile (8.5 g, 31.9% yield) was obtained as a white solid. $R_f = 0.5$ (PE: EtOAc = 3: 1). ^1H NMR (400 MHz, CDCl_3) δ 7.66 (d, $J = 1.6$ Hz, 1H), 7.61 (dd, $J = 1.6$, 8.8 Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 4.84 - 4.77 (m, 1H), 3.76 (q, $J = 6.4$ Hz, 2H), 2.90 (t, $J = 6.4$ Hz, 2H).

Step 2: Synthesis of 3-((5-bromobenzo[d]isoxazol-3-yl)amino)propanamide

To a solution of 3-((5-bromobenzo[d]isoxazol-3-yl)amino)propanenitrile (7.00 g, 26.3 mmol) in TFA (20 mL) was added H_2SO_4 (4 mL). The mixture was stirred at 25 °C for 3 hrs. The mixture was poured into water (40 mL) and extracted with ethyl acetate (40 mL x 2). The mixture was diluted with ethyl acetate (40 mL), basified with Na_2CO_3 (s) to pH = 9~10 and filtered. The filter cake was washed with brine (30 mL), which was redissolved in a solution consisting of CAN (30 mL) and H_2O (15 mL) and lyophilized to give the crude product. Compound 3-((5-bromobenzo[d]isoxazol-3-yl)amino)propanamide

(22.0 g, crude) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 1.6 Hz, 1H), 7.77 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.49 (br. s., 1H), 7.22 (t, *J* = 5.6 Hz, 1H), 6.98 (br. s., 1H), 3.54 (q, *J* = 6.8 Hz, 2H), 2.55 (t, *J* = 6.8 Hz, 2H).

Step 3: Synthesis of *tert*-butyl (*S*)-4-((3-((3-amino-3-oxopropyl)amino)benzo

5 [d]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate

A mixture of 3-((5-bromobenzo[d]isoxazol-3-yl)amino)propanamide (3.00 g, 10.6 mmol), potassium [(3*S*)-4-*tert*-butoxycarbonyl-3-methyl-piperazin-1-yl]methyl-trifluoro-boranuide (3.38 g, 10.6 mmol), RuPhos Pd G3 (883 mg, 1.06 mmol), Cs₂CO₃ (6.88 g, 21.1 mmol) in toluene (30 mL) and H₂O (6 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 12 hrs under N₂ atmosphere. The mixture was poured into water (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% Methanol/Dichloromethane gradient @ 40 mL/min). Compound *tert*-butyl (*S*)-4-((3-((3-amino-3-oxopropyl)amino)benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate (880 mg, 20.0% yield) was obtained as a yellow oil. R_f = 0.2 (Dichloromethane: Methanol = 10: 1). ¹H NMR (400 MHz, CDCl₃) δ 7.50 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.45 - 7.40 (m, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 5.68 (br. s., 1H), 5.44 (br. s., 1H), 5.15 - 5.08 (m, 1H), 4.23 - 4.16 (m, 1H), 3.84 - 3.72 (m, 3H), 3.60 - 3.44 (m, 2H), 3.16 - 3.05 (m, 1H), 2.77 - 2.68 (m, 3H), 2.60 - 2.53 (m, 1H), 2.17 - 2.12 (m, 1H), 2.04 - 1.97 (m, 1H), 1.48 - 1.44 (m, 9H), 1.25 - 1.21 (m, 3H).

Step 4: Synthesis of *tert*-butyl (*S*)-4-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*))-yl)benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl (*S*)-4-((3-((3-amino-3-oxopropyl)amino)benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate (840 mg, 2.01 mmol) in THF (8 mL) was added NaH (402 mg, 10.1 mmol, 60% purity) at 0 °C. The mixture was stirred at 0 °C for 0.5 hr. CDI (489 mg, 3.02 mmol) was added to the above solution at 0 °C. The mixture was stirred at 25 °C for 1.5 hrs. The mixture was diluted with ethyl acetate (20 mL), quenched with 2M AcOH(5 mL), and extracted with ethyl acetate (20 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol/Dichloromethane gradient @ 25 mL/min). Compound *tert*-butyl (*S*)-4-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*))-yl)

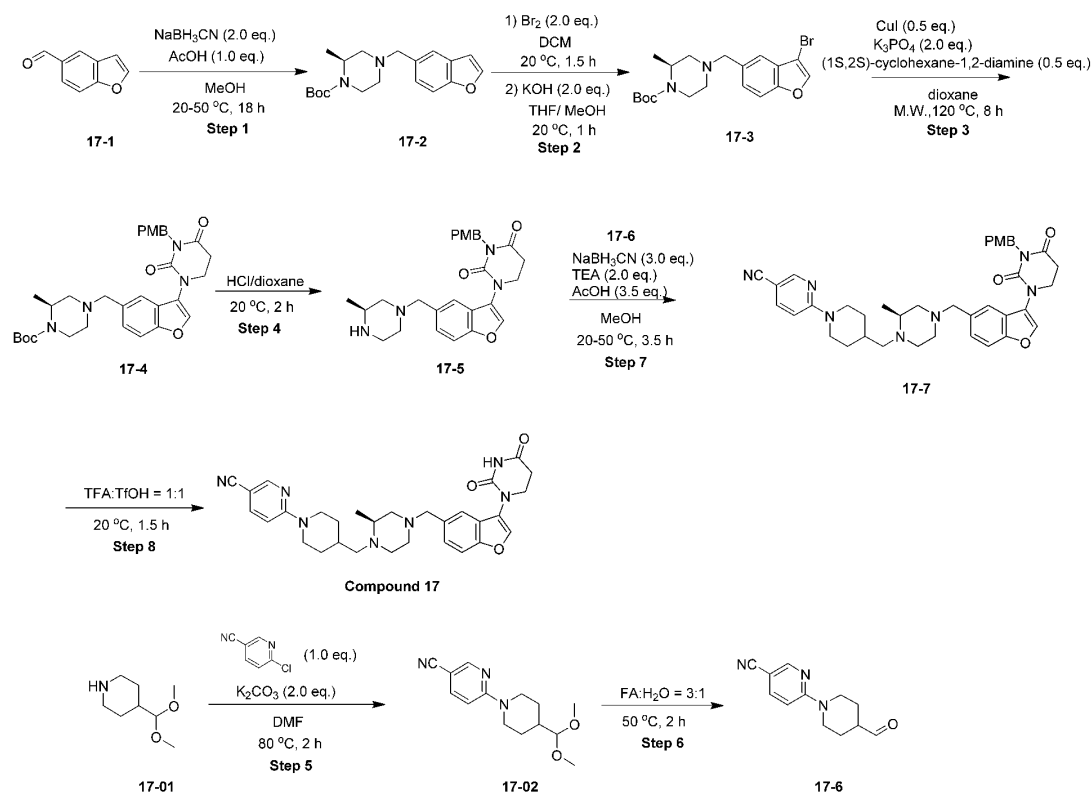
benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate (410 mg, 38.6% yield) was obtained as a yellow oil. $R_f = 0.4$ (Dichloromethane: Methanol = 10: 1). ^1H NMR (400 MHz, CDCl_3) δ 7.75 (s, 1H), 7.63 (d, $J = 8.8$ Hz, 1H), 7.50 (d, $J = 8.8$ Hz, 1H), 4.24 - 4.22 (m, 1H), 3.91 (dd, $J = 6.8, 13.4$ Hz, 2H), 3.85 - 3.76 (m, 1H), 3.75 - 3.67 (m, 2H), 3.65 - 3.48 (m, 2H), 3.15 - 3.06 (m, 1H), 2.95 - 2.89 (m, 2H), 2.78 - 2.72 (m, 1H), 2.61 - 2.55 (m, 1H), 2.18 - 2.13 (m, 1H), 1.45 (s, 9H), 1.24 - 1.23 (m, 3H).

Step 5: Synthesis of (S)-1-(5-((3-methylpiperazin-1-yl)methyl)benzo[d]isoxazol-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

To a solution of *tert*-butyl (S)-4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-6-fluorobenzo[d]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate (410 mg, 924 μmol) in DCM (2 mL) was added HCl/dioxane (2 mL). The mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to afford the crude product, which was used into the next step without further purification. Compound (S)-1-(5-((3-methylpiperazin-1-yl)methyl)benzo[d]isoxazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (351 mg, HCl salt, crude) was obtained as a white solid. LCMS (ESI^+): m/z 344.2 $[\text{M}+\text{H}]^+$.

Step 6: Synthesis of Compound 16: (S)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile

To a solution of (S)-1-(5-((3-methylpiperazin-1-yl)methyl)benzo[d]isoxazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (50 mg, 145.61 μmol) in DMF (1 mL), Et_3N (36.84 mg, 364.03 μmol) was added. Then 6-(4-formylpiperidin-1-yl)nicotinonitrile (31.34 mg, 145.61 μmol) and AcOH (30.6 mg, 510 μmol) were added to the above solution. The mixture was stirred at 50 °C for 12 hrs. Then the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure, which was purified by reversed-phase HPLC (Condition: 10% to 40% of phase B (Phase A: water (FA), Phase B: MeCN, Flow rate: 20 mL/min) and directly dry-freezing. Compound (S)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile (4.7 mg, 6.0% yield) was obtained as a white solid. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 10.91 (br. s., 1H), 8.44 (d, $J = 2.4$ Hz, 1H), 7.79 (dd, $J = 2.4, 9.2$ Hz, 1H), 7.72 (s, 1H), 7.69 - 7.65 (m, 1H), 7.61 - 7.56 (m, 1H), 6.90 (d, $J = 9.2$ Hz, 1H), 4.46 - 4.34 (m, 2H), 4.07 (t, $J = 6.8$ Hz, 2H), 3.56 - 3.49 (m, 2H), 2.99 - 2.86 (m, 2H), 2.83 - 2.76 (m, 3H), 2.63 - 2.54 (m, 2H), 2.35 - 2.26 (m, 1H), 2.20 - 2.10 (m, 2H), 1.96 - 1.74 (m, 5H), 1.71 - 1.64 (m, 1H), 1.11 - 0.93 (m, 2H), 0.90 (d, $J = 6.4$ Hz, 3H). LCMS (ESI^+): m/z 543.2 $[\text{M}+\text{H}]^+$.

Example 11: Preparation of Compound 17:**(S)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzofuran-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile****Step 1: Synthesis of *tert*-butyl (S)-4-(benzofuran-5-ylmethyl)-2-methylpiperazine-1-carboxylate**

To a solution of benzofuran-5-carbaldehyde (2.00 g, 13.7 mmol) and *tert*-butyl (S)-2-methylpiperazine-1-carboxylate (2.74 g, 13.7 mmol) in MeOH (30 mL), AcOH (822 mg, 13.7 mmol, 783.4 μ L) was added. The mixture was stirred at 50 °C for 2 hrs. Then the mixture was cooled to 20 °C, NaBH₃CN (1.72 g, 27.4 mmol) was added. The mixture was stirred at 20 °C for 16 hrs. The mixture was concentrated to remove solvent. The residue was diluted with EtOAc (30 mL) and washed with water (30 mL). After partition, the aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc: PE gradient @ 40 mL/min) to give *tert*-butyl (S)-4-(benzofuran-5-ylmethyl)-2-methylpiperazine-1-carboxylate (2.30 g, 43.2% yield) as a colorless oil. R_f = 0.55 (PE: EtOAc = 5: 1). ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* =

2.0 Hz, 1H), 7.55 - 7.51 (m, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.29 (dd, $J = 1.6, 8.4$ Hz, 1H), 6.74 (dd, $J = 0.8, 2.4$ Hz, 1H), 4.24 - 4.15 (m, 1H), 3.85 - 3.72 (m, 1H), 3.64 - 3.56 (m, 1H), 3.52 - 3.45 (m, 1H), 3.18 - 3.05 (m, 1H), 2.77 (d, $J = 11.2$ Hz, 1H), 2.61 (d, $J = 11.2$ Hz, 1H), 2.14 (dd, $J = 4.0, 11.2$ Hz, 1H), 2.04 - 1.96 (m, 1H), 1.45 (s, 9H), 1.24 (d, $J = 6.8$ Hz, 3H).

Step 2: Synthesis of *tert*-butyl (*S*)-4-((3-bromobenzofuran-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl (*S*)-4-(benzofuran-5-ylmethyl)-2-methylpiperazine-1-carboxylate (1.20 g, 3.63 mmol) in DCM (15 mL), Br₂ (1.16 g, 7.26 mmol) was added. The mixture was stirred at 20 °C for 1.5 hrs. The reaction was diluted with water (30 mL). The resulting mixture was extracted with DCM (30 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was dissolved in THF (15 mL) and a solution of KOH (407.6 mg, 7.26 mmol) in MeOH (4 mL) was added. The mixture was stirred at 20 °C for 1 hr. The mixture was diluted with EtOAc (30 mL) and washed with water (30 mL). After partition, the aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethylacetate/Petroleum ether gradient @ 25 mL/min) to give *tert*-butyl (*S*)-4-((3-bromobenzofuran-5-yl)methyl)-2-methylpiperazine-1-carboxylate (370 mg, 18.9% yield) as a colorless oil. $R_f = 0.4$ (PE: EtOAc = 5: 1). LCMS (ESI⁺): m/z 411.1 [M+H]⁺.

Step 3: Synthesis of *tert*-butyl (*S*)-4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzofuran-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of 3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (254 mg, 1.08 mmol) and *tert*-butyl (*S*)-4-((3-bromobenzofuran-5-yl)methyl)-2-methylpiperazine-1-carboxylate (370 mg, 904 μmol) in dioxane (5 mL), CuI (86.1 mg, 452 μmol), K₃PO₄ (384 mg, 1.81 mmol) and (1*S*,2*S*)-cyclohexane-1,2-diamine (51.6 mg, 452 μmol) were added. The mixture was stirred at 120 °C for 8 hrs under microwave. The mixture was filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethylacetate/Petroleum ether gradient @ 20 mL/min) [TLC (acidic silica gel, PE: EtOAc = 1: 1), $R_f = 0.5$] to give *tert*-butyl (*S*)-4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzofuran-5-yl)methyl)-2-methylpiperazine-1-carboxylate

ylate (250 mg, 49.2% yield) was obtained as a yellow oil. $R_f = 0.5$ (PE: EtOAc = 1: 1). LCMS (ESI⁺): m/z 563.2 [M+H]⁺.

Step 4: Synthesis of (S)-3-(4-methoxybenzyl)-1-(5-((3-methylpiperazin-1-yl)methyl)benzofuran-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

5 A mixture *tert*-butyl (S)-4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl) benzofuran-5-yl)methyl)-2-methylpiperazine-1-carboxylate (250 mg, 444.3 μ mol) and HCl/dioxane (4 M, 3 mL) was stirred at 20 °C for 2 hrs. The mixture was concentrated under reduced pressure to give (S)-3-(4-methoxybenzyl)-1-(5-((3-methylpiperazin-1-yl)methyl)benzofuran-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (220 mg, crude, HCl salt) was obtained as a yellow oil, which was used into the next step without further purification. LCMS (ESI⁺): m/z 463.2 [M+H]⁺

Step 5: Synthesis of 6-(4-(dimethoxymethyl)piperidin-1-yl)nicotinonitrile

To a solution of 6-chloronicotinonitrile (435 mg, 3.14 mmol) in DMF (5 mL), K₂CO₃ (868 mg, 6.28 mmol) and 4-(dimethoxymethyl)piperidine (500 mg, 3.14 mmol) were added. The mixture was stirred at 80 °C for 2 hrs. The mixture was diluted with EtOAc (30 mL) and washed with brine (30 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% EA/PE gradient @ 30 mL/min) to give 6-(4-(dimethoxymethyl)piperidin-1-yl) nicotinonitrile (800 mg, 97.5% yield) as a white solid. $R_f = 0.27$ (PE: EtOAc = 5: 1). LCMS (ESI⁺): m/z 262.3 [M+H]⁺.

Step 6: Synthesis of 6-(4-formylpiperidin-1-yl)nicotinonitrile

To a solution of 6-(4-(dimethoxymethyl)piperidin-1-yl)nicotinonitrile (200 mg, 765.4 μ mol) in H₂O (0.7 mL) was added FA (2.44 g, 53.0 mmol, 2 mL). The mixture was stirred at 50 °C for 2 hrs. The mixture was concentrated under reduced pressure to give 6-(4-formylpiperidin-1-yl)nicotinonitrile (160 mg, crude) was obtained as a yellow oil. $R_f = 0.38$ (PE: EtOAc = 2: 1). ¹H NMR (400 MHz, CDCl₃) δ 9.71 (s, 1H), 8.40 (d, $J = 2.0$ Hz, 1H), 7.61 (dd, $J = 2.4, 9.2$ Hz, 1H), 6.62 (d, $J = 9.2$ Hz, 1H), 4.30 - 4.20 (m, 2H), 3.29 - 3.20 (m, 2H), 2.67 - 2.53 (m, 1H), 2.07 - 1.98 (m, 2H), 1.75 - 1.66 (m, 2H).

Step 7: Synthesis of (S)-6-(4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzofuran-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile

To a solution of (S)-3-(4-methoxybenzyl)-1-(5-((3-methylpiperazin-1-yl)methyl)benzofuran-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (70 mg, 151 μ mol) in MeOH (1 mL) was added TEA (30.6 mg, 302.7 μ mol, 42.13 μ L) and the mixture was

stirred at 20 °C for 30 min. Then 6-(4-formylpiperidin-1-yl)nicotinonitrile (48.9 mg, 227.0 μ mol) and AcOH (31.8 mg, 529.7 μ mol, 30.3 μ L) were added. The mixture was stirred at 50 °C for 2 hrs. The reaction mixture was cooled to 20 °C, and NaBH₃CN (28.5 mg, 454.0 μ mol) was added. The mixture was stirred at 20 °C for 1 hr. The mixture was concentrated

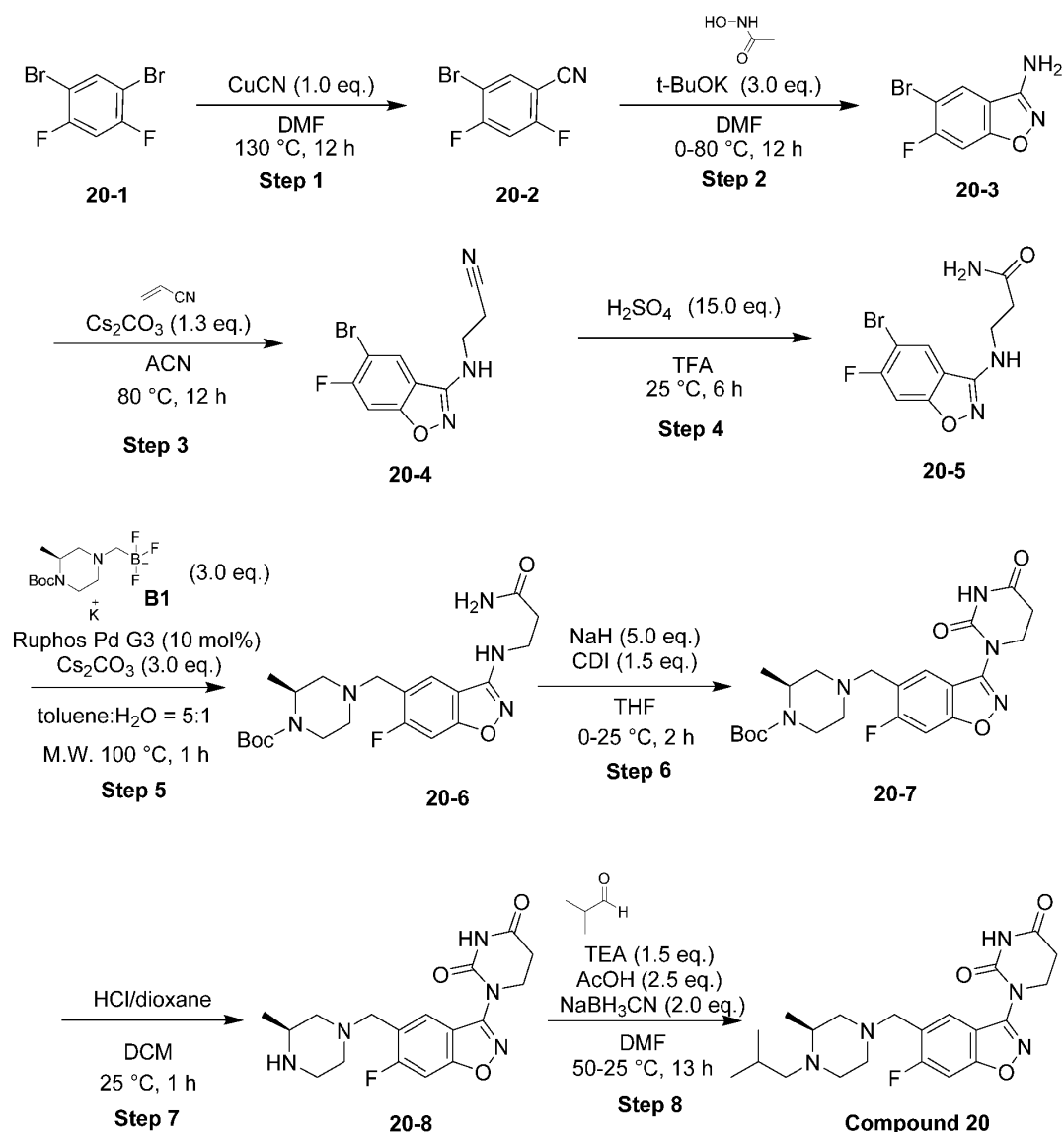
- 5 under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM @ 20 mL/min) to give (S)-6-(4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzofuran-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile (150 mg, 74.9% yield) as a colorless oil. R_f = 0.4
- 10 (Dichloromethane: Methanol = 10: 1). LCMS (ESI⁺): m/z 662.3 [M+H]⁺

Step 8: Synthesis of compound 17: (S)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzofuran-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile

- To a solution of (S)-6-(4-((4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzofuran-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile (150 mg, 227 μ mol) in TFA (0.5 mL) was added TfOH (848 mg, 5.65 mmol, 0.5 mL). The mixture was stirred at 20 °C for 1.5 hrs. The mixture was adjusted pH=7~8 with sat. NaHCO₃ aqueous solution. The resulting mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). After partition, the aqueous
- 20 layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-TLC. The crude product was purified by prep-HPLC (Column: Kromasil 100-5-C18 30*150 mm, Mobile Phase A: water (0.01% FA), Mobile Phase B: acetonitrile, 25 mL/min, gradient condition from 10% B to 50%) to give
- 25 (S)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzofuran-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile (5.72 mg, 4.55% yield) as a white solid. R_f = 0.52 (Dichloromethane: Methanol = 10: 1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.55 (br. s, 1H), 8.44 (d, *J* = 2.4 Hz, 1H), 8.11 (s, 1H), 7.79 (dd, *J* = 2.4, 9.2 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.49 (s, 1H), 7.30 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.90 (d, *J* = 9.2 Hz, 1H), 4.45 - 4.36 (m, 2H), 3.84 (t, *J* = 6.8 Hz, 2H), 3.53 - 3.52 (m, 2H), 2.99 - 2.86 (m, 3H), 2.84 - 2.76 (m, 3H), 2.66 - 2.55 (m, 2H), 2.47 - 2.30 (m, 2H), 2.25 - 2.10 (m, 2H), 1.99 - 1.88 (m, 2H), 1.87 - 1.82 (m, 1H), 1.72 - 1.62 (m, 1H), 1.11 - 0.94 (m, 2H), 0.92 (d, *J* = 6.0 Hz, 3H). LCMS (ESI⁺): m/z 542.5 [M+H]⁺.
- 30

35 **Example 12: Preparation of compound 20:**

(S)-1-(6-fluoro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)benzo[d]isoxazol-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



Step 1: Synthesis of 5-bromo-2,4-difluorobenzonitrile

- 5 To a solution of 1,5-dibromo-2,4-difluorobenzene (1.0 g, 3.68 mmol) in DMF (10 mL) was added CuCN (330 mg, 3.68 mmol). The mixture was stirred at 130 °C for 12 hrs. The mixture was poured into water (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash
- 10 silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum gradient @ 30 mL/min). Compound 5-bromo-2,4-difluorobenzonitrile (220 mg, 27.4% yield) was obtained as a white solid. R_f = 0.6 (Petroleum ether: Ethyl acetate = 5:

1). ^1H NMR (400 MHz, CDCl_3) δ 7.92 - 7.83 (m, 1H), 7.12 - 7.03 (m, 1H).

Step 2: Synthesis of 5-bromo-6-fluorobenzo[d]isoxazol-3-amine

To a solution of ethanehydroxamic acid (3.10 g, 41.3 mmol) in DMF (30 mL) was added t-BuOK (1.0 M, 41.3 mL, 41.3 mmol) at 0°C. Then 5-bromo-2,4-difluorobenzonitrile (3.00 g, 13.8 mmol) in DMF (5 mL) was added to the above mixture. The mixture was stirred at 80°C for 12 hrs. The mixture was poured into water (40 mL) and extracted with ethyl acetate (40 mL x 2). The combined organic extracts were washed with brine (40 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Dichloromethane/Petroleum ether gradient @ 50 mL/min). Compound 5-bromo-6-fluorobenzo[d]isoxazol-3-amine (3.50 g, 55.1% yield) was obtained as a white solid. R_f = 0.3 (Petroleum ether: Dichloromethane = 1: 1). ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 6.4 Hz, 1H), 7.22 (d, J = 8 Hz, 1H), 6.90 (d, J = 10.4 Hz, 2H).

Step 3: Synthesis of 3-((5-bromo-6-fluorobenzo[d]isoxazol-3-yl)amino)propanenitrile

To a solution of 5-bromo-6-fluorobenzo[d]isoxazol-3-amine (1.7 g, 7.36 mmol) in ACN (35 mL) were added prop-2-enenitrile (430 mg, 8.10 mmol) and Cs_2CO_3 (3.12 g, 9.57 mmol) at 25 °C. The mixture was stirred at 80 °C for 3 hrs. The mixture was concentrated under reduced pressure, which was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ether gradient @ 30 mL/min). Compound 3-((5-bromo-6-fluorobenzo[d]isoxazol-3-yl)amino)propanenitrile (870 mg, 41.6% yield) was obtained as a colorless oil. R_f = 0.3 (Ethyl acetate/Petroleum ether = 1: 1). ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, J = 6.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 4.95 - 4.85 (m, 1H), 3.79 - 3.70 (m, 2H), 2.93 - 2.85 (m, 2H).

Step 4: Synthesis of 3-((5-bromo-6-fluorobenzo[d]isoxazol-3-yl)amino)propanamide

To a solution of 3-((5-bromo-6-fluorobenzo[d]isoxazol-3-yl)amino)propanenitrile (850 mg, 2.99 mmol) in TFA (8 mL) was added H_2SO_4 (4.49 g, 45.8 mmol). The mixture was stirred at 25 °C for 6 hrs. The mixture was adjusted pH=7~8 with sat. NaHCO_3 solution and extracted with ethyl acetate (20 mL x 3). The organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product, which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol/Dichloromethane gradient @ 20 mL/min). Compound 3-((5-bromo-6-fluorobenzo[d]isoxazol-3-yl)amino)propanamide (125 mg, 13.3% yield) was obtained as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, J = 6.4 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 5.56 - 5.45 (m, 1H), 5.41 - 5.30 (m, 1H), 5.23 - 5.13 (m, 1H), 3.71 - 3.65 (m, 2H), 2.71 - 2.63 (m, 2H).

Step 5: Synthesis of *tert*-butyl (*S*)-4-((3-((3-amino-3-oxopropyl)amino)-6-fluorobenzo[*d*]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate

3-((5-bromo-6-fluorobenzo[*d*]isoxazol-3-yl)amino)propanamide (300 mg, 993 μ mol), potassium [(3*S*)-4-*tert*-butoxycarbonyl-3-methyl-piperazin-1-yl]methyl-trifluoro-boranuide (954 mg, 2.98 mmol), Cs₂CO₃ (971 mg, 2.98 mmol) in toluene (4 mL) and H₂O (0.8 mL) were added to a microwave tube before sparged with N₂ for 5 min, then treated with RuPhos Pd G3 (83.1 mg, 99.3 μ mol). The mixture was sprayed with N₂ for another 5 minutes and then stirred at 100 °C under microwave irradiation for 1 hr. The mixture was poured into water (10 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol/Dichloromethane gradient @ 20 mL/min). Compound *tert*-butyl (*S*)-4-((3-((3-amino-3-oxopropyl)amino)-6-fluorobenzo[*d*]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate (180 mg, 89.7% yield) was obtained as a yellow oil. R_f = 0.5 (Dichloromethane/Methanol = 10:1). ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 6.4 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 5.59 - 5.49 (m, 1H), 5.43 - 5.34 (m, 1H), 5.24 - 5.14 (m, 1H), 4.24 - 4.16 (m, 1H), 3.76 - 3.68 (m, 4H), 3.00 - 2.88 (m, 2H), 2.82 - 2.75 (m, 1H), 2.72 - 2.65 (m, 4H), 2.63 - 2.57 (m, 1H), 1.46 (s, 9H), 1.25 - 1.22 (m, 3H).

Step 6: Synthesis of *tert*-butyl (*S*)-4-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-fluorobenzo[*d*]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl (*S*)-4-((3-((3-amino-3-oxopropyl)amino)-6-fluorobenzo[*d*]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate (110 mg, 253 μ mol) in THF (3 mL) was added NaH (50.5 mg, 1.26 mmol, 60% purity) at 0 °C. The mixture was stirred at 0 °C for 0.5 hr. CDI (61.4 mg, 379 μ mol) was added to the above solution. The mixture was stirred at 25 °C for 1.5 hrs. The mixture was poured into 2M AcOH (5 mL) and extracted with ethyl acetate (5 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Methanol/Dichloromethane ether gradient @ 20mL/min). Compound *tert*-butyl (*S*)-4-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-fluorobenzo[*d*]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate (80.0 mg, 71.2% yield) was obtained as a colorless oil. R_f = 0.4 (Dichloromethane/Methanol = 10:1). LCMS (ESI⁺): *m/z* 462.4 [M+H]⁺.

Step 7: Synthesis of (*S*)-1-(6-fluoro-5-((3-methylpiperazin-1-yl)methyl)benzo[*d*]isoxazol-3-yl) dihydropyrimidine-2,4(1*H*,3*H*)-dione

To a solution of *tert*-butyl (*S*)-4-((3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-6-fluorobenzo[*d*]isoxazol-5-yl)methyl)-2-methylpiperazine-1-carboxylate (80.0 mg, 173 μ mol) in DCM (2 mL) and 4 M HCl/dioxane (2 mL) was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to afford the crude product, which was used into the next step without further purification. Compound (*S*)-1-(6-fluoro-5-((3-methylpiperazin-1-yl)methyl)benzo[*d*]isoxazol-3-yl) dihydropyrimidine-2,4(1*H*,3*H*)-dione (68.0 mg, HCl, crude) was obtained as a white solid. LCMS (ESI⁺): *m/z* 362.3 [M+H]⁺.

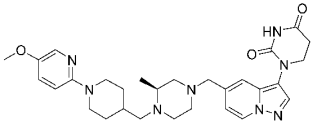
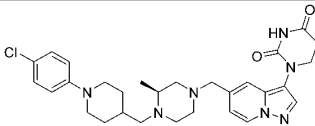
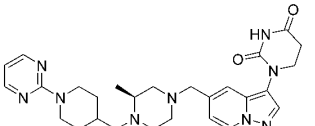
Step 8: Synthesis of compound 14: (*S*)-1-(6-fluoro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)benzo[*d*]isoxazol-3-yl) dihydropyrimidine-2,4(1*H*,3*H*)-dione

(*S*)-1-(6-fluoro-5-((3-methylpiperazin-1-yl)methyl)benzo[*d*]isoxazol-3-yl) dihydropyrimidine-2,4(1*H*,3*H*)-dione (68.0 mg, 170 μ mol, HCl) in DMF (2 mL) was added Et₃N (25.9 mg, 256 μ mol) and stirred for 5 min. Then 2-methylpropanal (18.5 mg, 256 μ mol) and AcOH (25.7 mg, 427 μ mol) were added to the above mixture and stirred at 50 °C for 12 hrs. The mixture was cooled to 25 °C and added NaBH₃CN (21.5 mg, 342 μ mol). Then the solution was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure, which was purified by reversed-phase HPLC (Condition: 10% to 40% of phase B (Phase A: water (FA), Phase B: MeCN, Flow rate: 20 mL/min) and directly dry-freezing. Compound (*S*)-1-(6-fluoro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)benzo[*d*]isoxazol-3-yl) dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.61 mg, 0.85% yield) was obtained as a yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ 10.93 (br. s., 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 9.6 Hz, 1H), 4.12 - 4.01 (m, 2H), 3.57 - 3.52 (m, 2H), 2.83 - 2.77 (m, 2H), 2.76 - 2.65 (m, 1H), 2.63 - 2.52 (m, 2H), 2.36 - 2.29 (m, 2H), 2.24 - 2.17 (m, 1H), 2.12 - 2.05 (m, 1H), 1.98 - 1.91 (m, 1H), 1.86 - 1.78 (m, 1H), 1.74 - 1.63 (m, 1H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 6H). LCMS (ESI⁺): *m/z* 418.3 [M+H]⁺.

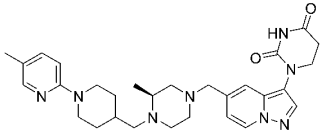
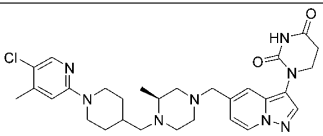
Example 13: The following compounds in Table 3 were prepared by the method of compound 6 with the appropriate aldehyde.

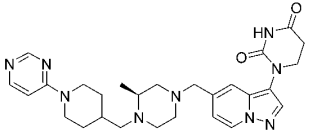
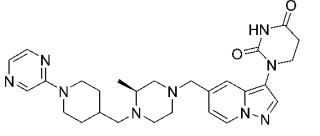
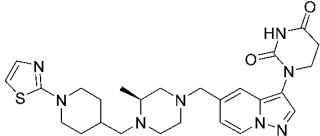
Table 3

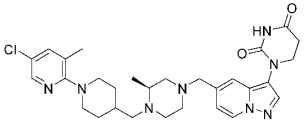
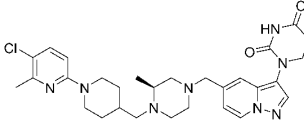
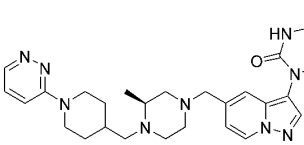
No.	Structure	Compound name and characterization
21		(<i>S</i>)-4-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2 <i>H</i>)-yl)pyrazolo[1,5- <i>a</i>]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)-2-fluorobenzonitrile ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.44 (s, 1H), 8.57 (d,

		$J = 7.1$ Hz, 1H), 8.01 (s, 1H), 7.54 (t, $J = 8.6$ Hz, 1H), 7.44 (s, 1H), 7.04 – 6.68 (m, 3H), 4.05 – 3.87 (m, 2H), 3.77 (t, $J = 6.7$ Hz, 3H), 3.01 – 2.68 (m, 5H), 2.57 (d, $J = 12.6$ Hz, 3H), 2.48 – 2.32 (m, 2H), 2.19 (t, $J = 9.7$ Hz, 2H), 1.94 (dd, $J = 12.7, 5.0$ Hz, 2H), 1.88 – 1.61 (m, 3H), 1.37 – 0.99 (m, 2H), 0.93 (d, $J = 6.1$ Hz, 3H). LCMS (ESI⁺): m/z 559.47 [M+H]⁺.
22		(S)-1-(5-((4-((1-(5-methoxypyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.43 (s, 1H), 8.57 (d, $J = 7.2$ Hz, 1H), 8.00 (s, 1H), 7.85 (d, $J = 3.1$ Hz, 1H), 7.44 (s, 1H), 7.22 (dd, $J = 9.2, 3.1$ Hz, 1H), 6.88 (d, $J = 7.2$ Hz, 1H), 6.77 (d, $J = 9.2$ Hz, 1H), 4.08 (s, 2H), 3.77 (t, $J = 6.7$ Hz, 3H), 3.48 (d, $J = 19.8$ Hz, 2H), 2.77 (t, $J = 6.7$ Hz, 2H), 2.63 (dd, $J = 25.2, 11.8$ Hz, 2H), 2.33 (s, 1H), 2.18 (s, 2H), 1.94 (s, 2H), 1.81 (d, $J = 13.1$ Hz, 1H), 1.64 (d, $J = 12.3$ Hz, 2H), 1.29 (d, $J = 48.1$ Hz, 5H), 1.18 – 0.75 (m, 7H). LCMS (ESI⁺): m/z 547.6 [M+H]⁺.
23		(S)-1-(5-((4-((1-(4-chlorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹H NMR (400MHz, DMSO-<i>d</i>₆) δ 10.44 (br. s., 1H), 8.57 (d, $J = 7.2$ Hz, 1H), 8.01 (s, 1H), 7.45 (s, 1H), 7.19 (d, $J = 9.2$ Hz, 2H), 6.94 - 6.85 (m, 3H), 3.76 (t, $J = 6.8$ Hz, 2H), 3.65 (d, $J = 9.8$ Hz, 4H), 2.96 - 2.87 (m, 1H), 2.77 (t, $J = 6.8$ Hz, 2H), 2.70 - 2.57 (m, 5H), 2.49 - 2.39 (m, 1H), 2.38 - 2.25 (m, 2H), 2.16 - 1.98 (m, 2H), 1.87 - 1.79 (m, 1H), 1.72 - 1.61 (m, 2H), 1.26 - 1.07 (m, 2H), 0.99 (d, $J = 6.2$ Hz, 3H). LCMS (ESI⁺): m/z 550.4 [M+H]⁺.
24		(S)-1-(5-((3-methyl-4-((1-(pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.44 (br. s., 1H), 8.56 (d, $J = 7.2$ Hz, 1H),

		8.31 (d, $J = 4.8$ Hz, 2H), 8.00 (s, 1H), 7.43 (s, 1H), 6.88 (d, $J = 7.2$ Hz, 1H), 6.57 - 6.51 (m, 1H), 4.67 - 4.57 (m, 2H), 3.76 (t, $J = 6.4$ Hz, 2H), 3.47 - 3.44 (m, 2H), 2.88 - 2.75 (m, 5H), 2.63 - 2.54 (m, 2H), 2.48 - 2.43 (m, 1H), 2.41 - 2.32 (m, 1H), 2.27 - 2.15 (m, 2H), 1.99 - 1.88 (m, 2H), 1.86 - 1.78 (m, 1H), 1.77 - 1.70 (m, 1H), 1.69 - 1.61 (m, 1H), 1.09 - 0.95 (m, 2H), 0.93 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 518.4 [M+H] ⁺ .
25		(S)-1-(5-((4-((1-(5-chloropyrimidin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.44 (s, 1H), 8.57 (d, $J = 7.2$ Hz, 1H), 8.37 (s, 2H), 8.01 (s, 1H), 7.44 (s, 1H), 6.89 (dd, $J = 1.2, 7.2$ Hz, 1H), 4.62 - 4.49 (m, 2H), 3.77 (t, $J = 6.8$ Hz, 2H), 3.52 - 3.51 (m, 2H), 2.92 - 2.81 (m, 3H), 2.78 (t, $J = 6.8$ Hz, 2H), 2.66 - 2.55 (m, 2H), 2.48 - 2.33 (m, 2H), 2.28 - 2.17 (m, 2H), 2.04 - 1.90 (m, 2H), 1.88 - 1.72 (m, 2H), 1.70 - 1.63 (m, 1H), 1.11 - 0.96 (m, 2H), 0.94 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 552.4 [M+H] ⁺ .
26		(S)-1-(5-((4-((1-(2,4-difluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 10.43 (br. s., 1H), 8.58 (d, $J = 8$ Hz, 1H), 8.01 (s, 1H), 7.45 (s, 1H), 7.16 (d, $J = 15$ Hz, 1H), 6.94 - 6.85 (m, 3H), 3.76 (t, $J = 6.8$ Hz, 2H), 3.45 (d, $J = 10$ Hz, 2H), 3.2 (m, 2H), 2.78 (t, $J = 6.8$ Hz, 2H), 2.70 - 2.57 (m, 5H), 2.49 - 2.35 (m, 2H), 2.30 - 2.20 (m, 3H), 2.10 - 1.90 (m, 2H), 1.75 - 1.65 (m, 2H), 1.60 - 1.5 (m, 2H), 0.99 (d, $J = 6.2$ Hz, 3H). LCMS (ESI ⁺): m/z 552.4 [M+H] ⁺ .
27		(S)-1-(5-((4-((1-(4-chloropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.45 (br. s., 1H), 8.57 (d, $J = 7.2$

		Hz, 1H), 8.03 (d, $J = 5.2$ Hz, 1H), 8.01 (s, 1H), 7.46 - 7.43 (m, 1H), 6.91 - 6.86 (m, 2H), 6.63 (dd, $J = 1.6, 5.2$ Hz, 1H), 4.33 - 4.23 (m, 2H), 3.77 (t, $J = 6.8$ Hz, 2H), 3.46 - 3.46 (m, 2H), 2.84 - 2.75 (m, 5H), 2.65 - 2.56 (m, 2H), 2.48 - 2.45 (m, 1H), 2.40 - 2.33 (m, 1H), 2.26 - 2.15 (m, 2H), 1.99 - 1.89 (m, 2H), 1.86 - 1.77 (m, 1H), 1.77 - 1.62 (m, 2H), 1.11 - 0.96 (m, 2H), 0.94 (d, $J = 6.4$ Hz, 3H); LCMS (ESI ⁺): m/z 551.2 [M+H] ⁺ .
30		(S)-1-(5-((3-methyl-4-((1-(5-methylpyridin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.43 (br. s., 1H), 8.55 (d, $J = 7.2$ Hz, 1H), 7.99 (s, 1H), 7.92 - 7.87 (m, 1H), 7.42 (s, 1H), 7.31 (dd, $J = 2.0, 8.4$ Hz, 1H), 6.87 (dd, $J = 1.6, 7.2$ Hz, 1H), 6.70 (d, $J = 8.8$ Hz, 1H), 4.22 - 4.11 (m, 2H), 3.75 (t, $J = 6.8$ Hz, 2H), 3.45 - 3.44 (m, 2H), 3.33 - 3.13 (m, 2H), 2.76 (t, $J = 6.8$ Hz, 2H), 2.71 - 2.65 (m, 2H), 2.61 - 2.53 (m, 2H), 2.46 - 2.41 (m, 1H), 2.36 - 2.29 (m, 1H), 2.18 - 2.13 (m, 1H), 2.10 (s, 3H), 1.96 - 1.87 (m, 2H), 1.82 - 1.75 (m, 1H), 1.68 - 1.59 (m, 2H), 1.10 - 0.95 (m, 2H), 0.91 (d, $J = 6.2$ Hz, 3H); LCMS (ESI ⁺): m/z 531.4 [M+H] ⁺ .
31		(S)-1-(5-((4-((1-(5-chloro-4-methylpyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.45 (s, 1H), 8.57 (d, $J = 7.2$ Hz, 1H), 8.01 (s, 1H), 7.99 (s, 1H), 7.44 (s, 1H), 6.89 (dd, $J = 1.2, 7.2$ Hz, 1H), 6.82 (s, 1H), 4.27 - 4.16 (m, 2H), 3.77 (t, $J = 6.8$ Hz, 2H), 3.56 - 3.53 (m, 2H), 2.82 - 2.69 (m, 5H), 2.64 - 2.54 (m, 2H), 2.47 - 2.43 (m, 1H), 2.39 - 2.30 (m, 1H), 2.23 (s, 3H), 2.22 - 2.12 (m, 2H), 1.99 - 1.86 (m, 2H), 1.84 - 1.76 (m, 1H), 1.74 - 1.59 (m, 2H), 1.12 - 0.95 (m, 2H), 0.93 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 565.2 [M+H] ⁺ .

32		(<i>S</i>)-1-(5-((3-methyl-4-((1-(pyrimidin-4-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-<i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1<i>H</i>,3<i>H</i>)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.49 (br. s., 1H), 8.79 (s, 1H), 8.69 (d, <i>J</i> = 7.2 Hz, 1H), 8.30 (d, <i>J</i> = 7.2 Hz, 1H), 8.08 (s, 1H), 7.59 (s, 1H), 7.27 - 7.20 (m, 1H), 6.97 - 6.92 (m, 1H), 4.98 - 4.84 (m, 1H), 4.36 - 4.20 (m, 1H), 4.01 - 3.87 (m, 2H), 3.79 (t, <i>J</i> = 6.8 Hz, 2H), 3.32 - 2.96 (m, 11H), 2.78 (t, <i>J</i> = 6.8 Hz, 2H), 2.25 - 2.11 (m, 1H), 2.04 - 1.92 (m, 1H), 1.89 - 1.74 (m, 1H), 1.33 - 1.15 (m, 5H); LCMS (ESI⁺): <i>m/z</i> 518.4 [M+H]⁺.
33		(<i>S</i>)-1-(5-((3-methyl-4-((1-(pyrazin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-<i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1<i>H</i>,3<i>H</i>)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.45 (s, 1H), 8.57 (d, <i>J</i> = 7.2 Hz, 1H), 8.28 (s, 1H), 8.04 (d, <i>J</i> = 2.4 Hz, 1H), 8.01 (s, 1H), 7.76 (d, <i>J</i> = 2.4 Hz, 1H), 7.44 (s, 1H), 6.89 (dd, <i>J</i> = 1.2, 7.2 Hz, 1H), 4.35 - 4.26 (m, 2H), 3.77 (t, <i>J</i> = 6.8 Hz, 2H), 3.55 - 3.53 (m, 2H), 2.92 - 2.74 (m, 5H), 2.67 - 2.55 (m, 2H), 2.49 - 2.41 (m, 1H), 2.41 - 2.31 (m, 1H), 2.27 - 2.14 (m, 2H), 2.01 - 1.89 (m, 2H), 1.88 - 1.80 (m, 1H), 1.79 - 1.64 (m, 2H), 1.15 - 0.98 (m, 2H), 0.94 (d, <i>J</i> = 6.0 Hz, 3H); LCMS (ESI⁺): <i>m/z</i> 518.4 [M+H]⁺.
34		(<i>S</i>)-1-(5-((3-methyl-4-((1-(thiazol-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-<i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1<i>H</i>,3<i>H</i>)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.50 (br. s., 1H), 8.72 (d, <i>J</i> = 7.2 Hz, 1H), 8.11 (s, 1H), 8.02 - 7.90 (m, 1H), 7.37 (d, <i>J</i> = 4.0 Hz, 1H), 7.29 - 7.22 (m, 1H), 7.04 (d, <i>J</i> = 4.4 Hz, 1H), 4.49 - 4.34 (m, 2H), 4.07 - 3.93 (m, 2H), 3.81 - 3.79 (m, 2H), 3.47 - 3.37 (m, 8H), 3.36 - 3.24 (m, 2H), 2.99 - 2.90 (m, 1H), 2.80 (t, <i>J</i> = 6.8 Hz, 2H), 2.29 - 2.11

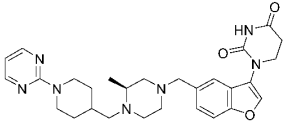
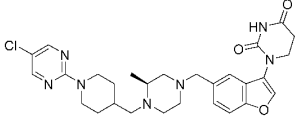
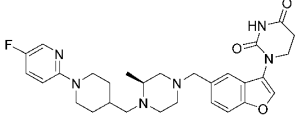
		(m, 2H), 1.97 - 1.80 (m, 1H), 1.48 - 1.31 (m, 5H); LCMS (ESI ⁺): m/z 523.4 [M+H] ⁺ .
35		(S)-1-(5-((4-((1-(5-chloro-3-methylpyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.43 (br. s., 1H), 8.56 (d, <i>J</i> = 7.2 Hz, 1H), 8.11 - 8.05 (m, 1H), 8.00 (s, 1H), 7.63 - 7.56 (m, 1H), 7.43 (s, 1H), 6.92 - 6.84 (m, 1H), 3.76 (t, <i>J</i> = 6.8 Hz, 2H), 3.50 - 3.49 (m, 2H), 3.36 - 3.34 (m, 2H), 2.82 - 2.74 (m, 3H), 2.72 - 2.54 (m, 5H), 2.39 - 2.31 (m, 1H), 2.24 - 2.17 (m, 5H), 2.01 - 1.90 (m, 2H), 1.88 - 1.80 (m, 1H), 1.72 - 1.65 (m, 1H), 1.63 - 1.56 (m, 1H), 1.25 - 1.14 (m, 2H), 0.95 (d, <i>J</i> = 6.0 Hz, 3H); LCMS (ESI ⁺): m/z 565.5 [M+H] ⁺ .
37		(S)-1-(5-((4-((1-(5-chloro-6-methylpyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.45 (br. s., 1H), 8.57 (d, <i>J</i> = 7.2 Hz, 1H), 8.01 (s, 1H), 7.48 - 7.43 (m, 2H), 6.89 (dd, <i>J</i> = 1.2, 7.2 Hz, 1H), 6.65 (d, <i>J</i> = 9.2 Hz, 1H), 4.27 - 4.16 (m, 2H), 3.77 (t, <i>J</i> = 6.8 Hz, 2H), 3.50 - 3.48 (m, 2H), 2.83 - 2.73 (m, 5H), 2.63 - 2.55 (m, 2H), 2.45 - 2.43 (m, 1H), 2.37 - 2.32 (m, 4H), 2.23 - 2.13 (m, 2H), 1.98 - 1.89 (m, 2H), 1.84 - 1.77 (m, 1H), 1.75 - 1.61 (m, 2H), 1.11 - 0.95 (m, 2H), 0.93 (d, <i>J</i> = 5.8 Hz, 3H); LCMS (ESI ⁺): m/z 565.4 [M+H] ⁺ .
38		(S)-1-(5-((3-methyl-4-((1-(pyridazin-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.46 (br. s., 1H), 8.60 - 8.56 (m, 1H), 8.48 (dd, <i>J</i> = 1.2, 4.4 Hz, 1H), 8.01 (s, 1H), 7.44 (s, 1H), 7.31 (d, <i>J</i> = 4.4 Hz, 1H), 7.24 - 7.19 (m, 1H), 6.89 (dd, <i>J</i> = 1.6, 7.2 Hz, 1H), 4.39 - 4.30 (m, 2H), 3.77 (t, <i>J</i> = 6.8

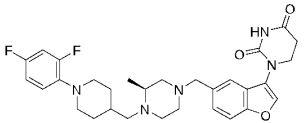
		Hz, 2H), 3.48 - 3.44 (m, 2H), 2.92 - 2.81 (m, 3H), 2.80 - 2.74 (m, 3H), 2.62 - 2.56 (m, 1H), 2.46 - 2.43 (m, 1H), 2.23 - 2.14 (m, 2H), 1.98 - 1.67 (m, 6H), 1.14 - 1.00 (m, 2H), 0.93 (d, $J = 6.4$ Hz, 3H); LCMS (ESI ⁺): m/z 518.2 [M+H] ⁺ .
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Example 14: The following compounds in **Table 4** were prepared by the method of **compound 17** with the appropriate aldehyde

Table 4

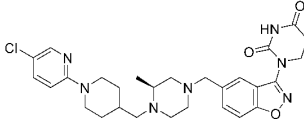
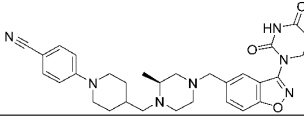
No.	Structure	Compound name and characterization
39		(S)-1-(5-(((4-((1-(5-chloropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)benzofuran-3-yl) dihydropyrimidin-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (br. s., 1H), 8.11 (s, 1H), 8.06 (d, $J = 2.8$ Hz, 1H), 7.56 - 7.52 (m, 2H), 7.48 (s, 1H), 7.30 (dd, $J = 1.6, 8.4$ Hz, 1H), 6.84 (d, $J = 9.2$ Hz, 1H), 4.25 - 4.18 (m, 2H), 3.84 (t, $J = 6.8$ Hz, 2H), 3.52 - 3.50 (m, 2H), 2.85 - 2.74 (m, 6H), 2.45 - 2.43 (m, 1H), 2.22 - 2.05 (m, 3H), 1.97 - 1.87 (m, 2H), 1.85 - 1.79 (m, 1H), 1.78 - 1.60 (m, 3H), 1.11 - 0.97 (m, 2H), 0.91 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 551.4 [M+H] ⁺ .
40		(S)-4-(4-(((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzofuran-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)benzonitrile ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.55 (s, 1H), 8.11 (s, 1H), 7.58 - 7.47 (m, 4H), 7.31 (d, $J = 8.8$ Hz, 1H), 6.58 (d, $J = 8.0$ Hz, 2H), 3.84 (t, $J = 6.8$ Hz, 2H), 3.56 - 3.54 (m, 2H), 3.50 - 3.49 (m, 2H), 2.96 - 2.83 (m, 3H), 2.83 - 2.75 (m, 3H), 2.72 - 2.57 (m, 3H), 2.41 - 2.31 (m, 2H), 2.29 - 2.19 (m, 2H), 2.16 - 2.09 (m, 1H), 2.03 - 1.89 (m, 1H), 1.69 - 1.51 (m, 3H), 1.01 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 541.4 [M+H] ⁺ .

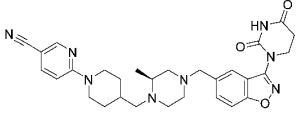
41		(S)-1-(5-((3-methyl-4-((1-(pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)benzofuran-3-yl) dihydropyrimidine-2,4(1H,3H)-dione, ^1H NMR (400 MHz, DMSO-d_6) δ 10.55 (br. s., 1H), 8.31 (d, $J = 4.8$ Hz, 2H), 8.10 (s, 1H), 7.56 - 7.51 (m, 1H), 7.48 (s, 1H), 7.32 - 7.27 (m, 1H), 6.55 (t, $J = 4.8$ Hz, 1H), 4.68 - 4.56 (m, 2H), 3.84 (t, $J = 6.4$ Hz, 2H), 3.51 - 3.50 (m, 1H), 3.49 - 3.49 (m, 1H), 2.85 - 2.74 (m, 5H), 2.62 - 2.53 (m, 2H), 2.46 - 2.40 (m, 1H), 2.35 - 2.27 (m, 1H), 2.21 - 2.08 (m, 2H), 1.94 - 1.79 (m, 3H), 1.77 - 1.69 (m, 1H), 1.68 - 1.59 (m, 1H), 1.08 - 0.92 (m, 2H), 0.91 (d, $J = 6.0$ Hz, 3H); LCMS (ESI$^+$): m/z 518.4 $[\text{M}+\text{H}]^+$.
42		(S)-1-(5-((4-((1-(5-chloropyrimidin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)benzofuran-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO-d_6) δ 10.55 (br. s., 1H), 8.37 (s, 2H), 8.10 (s, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.47 (s, 1H), 7.33 - 7.26 (m, 1H), 4.59 - 4.51 (m, 2H), 3.84 (t, $J = 6.4$ Hz, 2H), 3.51 - 3.50 (m, 1H), 3.49 - 3.49 (m, 1H), 2.94 - 2.74 (m, 5H), 2.63 - 2.53 (m, 2H), 2.46 - 2.41 (m, 1H), 2.35 - 2.27 (m, 1H), 2.21 - 2.08 (m, 2H), 1.94 - 1.79 (m, 3H), 1.77 - 1.69 (m, 1H), 1.68 - 1.61 (m, 1H), 1.09 - 0.92 (m, 2H), 0.90 (d, $J = 6.0$ Hz, 3H); LCMS (ESI$^+$): m/z 552.3 $[\text{M}+\text{H}]^+$.
43		(S)-1-(5-((4-((1-(5-fluoropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)benzofuran-3-yl) dihydropyrimidine-2,4(1H,3H)-dione, ^1H NMR (400 MHz, DMSO-d_6) δ 10.54 (br. s., 1H), 8.10 (s, 1H), 8.04 (d, $J = 3.2$ Hz, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.48 - 7.41 (m, 2H), 7.29 (d, $J = 8.8$ Hz, 1H), 6.82 (dd, $J = 3.2, 9.2$ Hz, 1H), 4.18 - 4.11 (m, 2H), 3.83 (t, $J = 6.4$ Hz, 2H), 3.55 - 3.53 (m, 2H), 2.80 - 2.67 (m, 5H), 2.60 - 2.53 (m, 2H), 2.46 - 2.44 (m, 1H), 2.34 - 2.27 (m, 1H), 2.19 - 2.11 (m, 2H), 1.95 - 1.86 (m, 2H), 1.84 - 1.78 (m, 1H), 1.68 - 1.60 (m, 2H), 1.14 - 0.96 (m, 2H), 0.91 (d, $J = 6.4$ Hz, 3H).

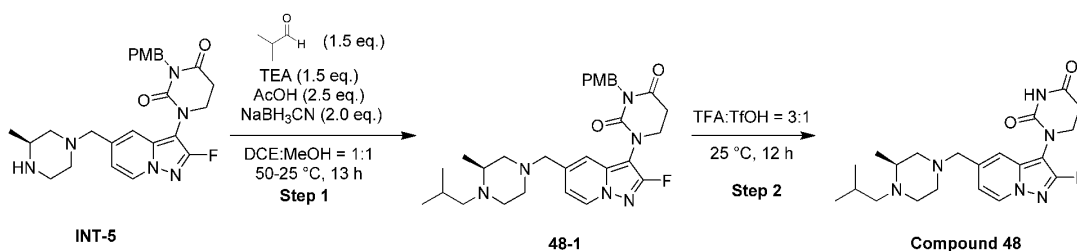
		3H); LCMS (ESI ⁺): m/z 535.5 [M+H] ⁺ .
44		(S)-1-(5-((4-((1-(2,4-difluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)benzofuran-3-yl)dihydropyrimidine-2,4(1H,3H)-dione ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.54 (br. s., 1H), 8.10 (s, 1H), 7.53 (d, <i>J</i> = 8.6 Hz, 1H), 7.47 (s, 1H), 7.29 (d, <i>J</i> = 8.6 Hz, 1H), 7.18 - 7.11 (m, 1H), 7.08 - 7.01 (m, 1H), 6.99 - 6.93 (m, 1H), 3.83 (t, <i>J</i> = 6.8 Hz, 2H), 3.52 - 3.48 (m, 1H), 3.24 - 3.21 (m, 3H), 2.78 (t, <i>J</i> = 6.8 Hz, 2H), 2.68 - 2.66 (m, 1H), 2.61 - 2.55 (m, 3H), 2.46 - 2.41 (m, 1H), 2.34 - 2.31 (m, 1H), 2.17 - 2.12 (m, 2H), 1.97 - 1.91 (m, 1H), 1.89 - 1.81 (m, 2H), 1.77 - 1.65 (m, 2H), 1.58 - 1.50 (m, 1H), 1.30 - 1.18 (m, 2H), 0.93 (d, <i>J</i> = 6.4 Hz, 3H); LCMS (ESI⁺): m/z 552.5 [M+H]⁺.

Example 15: The following compounds in **Table 5** were prepared by the method of **compound 20**

Table 5

No.	Structure	Compound name and characterization
45		(S)-1-(5-((4-((1-(5-chloropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)benzo[d]isoxazol-1-yl)dihydropyrimidine-2,4(1H,3H)-dione. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.90 (br. s., 1H), 8.09 - 8.04 (m, 1H), 7.72 (s, 1H), 7.70 - 7.65 (m, 1H), 7.62 - 7.57 (m, 1H), 7.56 - 7.51 (m, 1H), 6.88 - 6.80 (m, 1H), 4.27 - 4.17 (m, 2H), 4.07 (t, <i>J</i> = 6.8 Hz, 2H), 3.54 - 3.51 (m, 2H), 2.86 - 2.73 (m, 5H), 2.60 - 2.54 (m, 2H), 2.31 - 2.25 (m, 1H), 2.19 - 2.11 (m, 2H), 1.96 - 1.81 (m, 3H), 1.80 - 1.59 (m, 3H), 1.12 - 0.96 (m, 2H), 0.91 (d, <i>J</i> = 6.4 Hz, 3H); LCMS (ESI⁺): m/z 552.2 [M+H]⁺.
46		(S)-4-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-methylpiperazin-1-yl)methyl)benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)benzofuran-3-yl)dihydropyrimidine-2,4(1H,3H)-dione.

		ethyl)piperidin-1-yl)benzonitrile ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.91 (br. s., 1H), 8.44 (d, <i>J</i> = 2.4 Hz, 1H), 7.79 (dd, <i>J</i> = 2.4, 9.2 Hz, 1H), 7.72 (s, 1H), 7.69 - 7.65 (m, 1H), 7.61 - 7.56 (m, 1H), 6.90 (d, <i>J</i> = 9.2 Hz, 1H), 4.46 - 4.34 (m, 2H), 4.07 (t, <i>J</i> = 6.8 Hz, 2H), 3.56 - 3.49 (m, 2H), 2.99 - 2.86 (m, 2H), 2.83 - 2.76 (m, 3H), 2.63 - 2.54 (m, 2H), 2.35 - 2.26 (m, 1H), 2.20 - 2.10 (m, 2H), 1.96 - 1.74 (m, 5H), 1.71 - 1.64 (m, 1H), 1.11 - 0.93 (m, 2H), 0.90 (d, <i>J</i> = 6.4 Hz, 3H); LCMS (ESI ⁺): <i>m/z</i> 543.2 [M+H] ⁺ .
47		(S)-6-(4-(((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzo[d]isoxazol-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile ¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 10.91 (br. s., 1H), 8.44 (d, <i>J</i> = 2.4 Hz, 1H), 7.79 (dd, <i>J</i> = 2.4, 9.2 Hz, 1H), 7.72 (s, 1H), 7.69 - 7.65 (m, 1H), 7.61 - 7.56 (m, 1H), 6.90 (d, <i>J</i> = 9.2 Hz, 1H), 4.46 - 4.34 (m, 2H), 4.07 (t, <i>J</i> = 6.8 Hz, 2H), 3.56 - 3.49 (m, 2H), 2.99 - 2.86 (m, 2H), 2.83 - 2.76 (m, 3H), 2.63 - 2.54 (m, 2H), 2.35 - 2.26 (m, 1H), 2.20 - 2.10 (m, 2H), 1.96 - 1.74 (m, 5H), 1.71 - 1.64 (m, 1H), 1.11 - 0.93 (m, 2H), 0.90 (d, <i>J</i> = 6.4 Hz, 3H). LCMS (ESI ⁺): <i>m/z</i> 543.2 [M+H] ⁺ .

Example 16: Preparation of compound 48:**(S)-1-(2-fluoro-5-(((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

Step 1: Synthesis of**(*S*)-1-(2-fluoro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione**

To a solution of

- 5 (*S*)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (80.0 mg, 154 μ mol, HCl) in MeOH (2 mL) was added TEA (39.1 mg, 387 μ mol). Then AcOH (32.5 mg, 542 μ mol) and 2-methylpropanal (11.1 mg, 155 μ mol) were added to the above mixture and stirred at 50°C for 12 hrs. The NaBH₃CN (19.5 mg, 310 μ mol) was added to the mixture and stirred
10 at 25°C for 1 hr. The mixture was concentrated under reduced pressure, which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Methanol/Dichloromethane gradient @ 25 mL/min). Compound (*S*)-1-(2-fluoro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (30.0 mg, 28.2% yield) was
15 obtained as a yellow solid. R_f = 0.4 (Dichloromethane: Methanol = 10: 1). LCMS (ESI⁺): m/z 537.4 [M+H]⁺.

Step 2: Synthesis of**(*S*)-1-(2-fluoro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione**

- 20 To a solution of (*S*)-1-(2-fluoro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (30 mg, 55.9 μ mol) in TFA (1.5 mL) was added TfOH (0.5 mL). The mixture was stirred at 25 °C for 4 hrs. The mixture was adjusted pH=7~8 with aq. NaHCO₃ solution and concentrated in vacuo,
25 which was purified by reversed-phase HPLC (Condition: 25% to 40% of phase B (Phase A: water (0.01% FA), Phase B: MeCN, Flow rate: 20 mL/min) and directly dry-freezing. Compound (*S*)-1-(2-fluoro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (10.0 mg, 38.5% yield) was obtained as a white
30 solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.56 (br. s., 1H), 8.51 (d, J = 7.2 Hz, 1H), 7.53 - 7.44 (m, 1H), 6.96 (dd, J = 1.6, 7.2 Hz, 1H), 3.78 - 3.74 (m, 2H), 3.42 - 3.37 (m, 2H), 2.84 - 2.74 (m, 3H), 2.62 - 2.55 (m, 2H), 2.43 - 2.32 (m, 2H), 2.28 - 2.11 (m, 2H), 2.02 - 1.84 (m, 2H), 1.78 - 1.62 (m, 1H), 0.94 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 6.8 Hz, 6H). LCMS

(ESI⁺): m/z 417.2 [M+H]⁺.

Example 17: The following compounds in **Table 6** were prepared by the method of **compound 48**

5

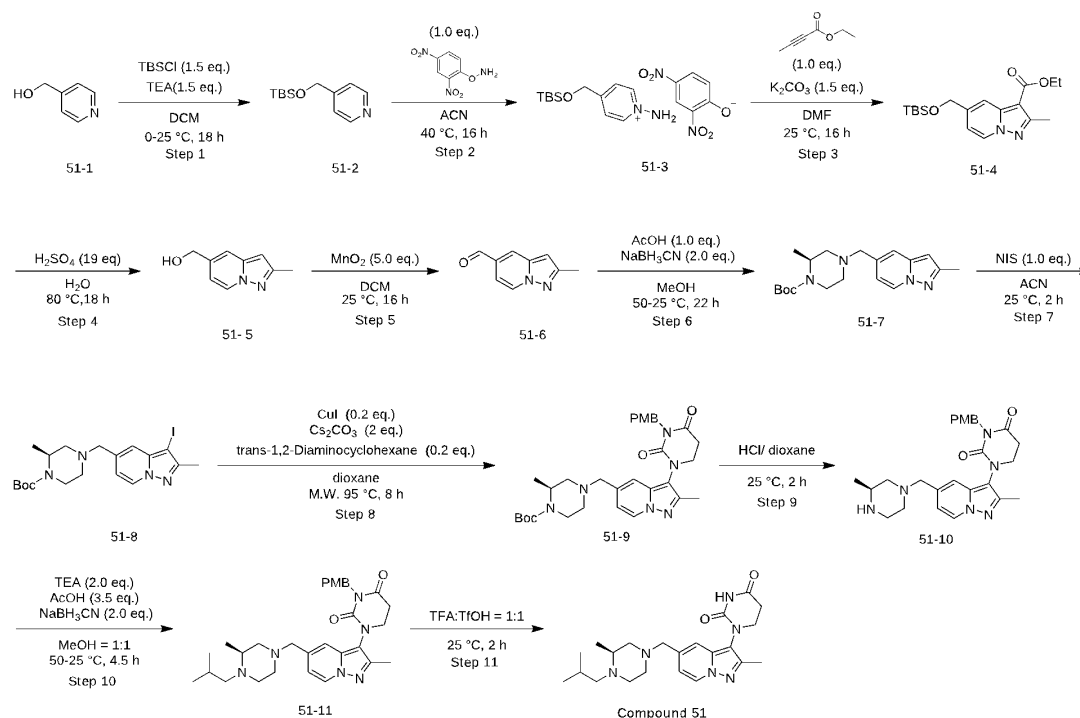
Table 6

No.	Structure	Compound name and characterization
49		1-(5-(((3S)-4-(2-cyclopropylpropyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione LCMS (ESI ⁺): m/z 443.5 [M+H] ⁺ .

Example 18: Preparation of compound 51:

(S)-1-(5-(((4-isobutyl-3-methylpiperazin-1-yl)methyl)-2-methylpyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

10



Step 1: Synthesis of 4-(((tert-butyl dimethylsilyl)oxy)methyl)pyridine

To a solution of 4-pyridylmethanol (10.0 g, 91.6 mmol) in DCM (100 mL) were added TEA (13.9 g, 137 mmol, 19.1 mL) and TBSCl (20.7 g, 137 mmol, 16.9 mL) at 0 °C.

15 The mixture was stirred at 25 °C for 18 hrs. The reaction mixture was diluted with DCM

(200 mL) and washed with water (200 mL). After partition, the aqueous layer was extracted with DCM (200 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethylacetate/Petroleum ether gradient @ 60 mL/min). Compound 4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine (10.0 g, 48.9% yield) was obtained as a light yellow oil. R_f = 0.33 (Petroleum ether: Ethyl acetate = 3:1). LCMS (ESI⁺): m/z 224.4 [M+H]⁺.

Step 2: Synthesis of

10 1-amino-4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-1-ium;2,4-dinitrophenolate

To a solution of 4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine (10.0 g, 44.8 mmol) in MeCN (50 mL) was added O-(2,4-dinitrophenyl)hydroxylamine (8.91 g, 44.8 mmol). The mixture was stirred at 40 °C for 16 hrs. The mixture was concentrated under reduced pressure. The crude product

15 1-amino-4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-1-ium; 2,4-dinitrophenolate (19 g, crude) was obtained as a brown oil, which was used into the next step without further purification.

Step 3: Synthesis of ethyl

20 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylpyrazolo[1,5-*a*]pyridine-3-carboxylate

To a solution of 1-amino-4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-1-ium;2,4-dinitrophenolate (24.7 g, 58.5 mmol) in DMF (100 mL) were added K₂CO₃ (12.1 g, 87.7 mmol) and ethyl but-2-ynoate (6.55 g, 58.5 mmol, 6.81 mL). The mixture was stirred at 25 °C for 16 hrs.

25 The mixture was diluted with EtOAc (200 mL) and washed with brine (200 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethylacetate/Petroleum ether gradient @ 80 mL/min). Compound ethyl

30 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylpyrazolo[1,5-*a*]pyridine-3-carboxylate (5.2 g, 25.5% yield) was obtained as a yellow oil. R_f = 0.4 (Petroleum ether: Ethyl acetate = 10:1). ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, J = 7.2 Hz, 1H), 7.88 (s, 1H), 6.69 (dd, J =

1.6, 7.2 Hz, 1H), 4.66 (s, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 2.53 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 0.83 (s, 9H), 0.00 (s, 6H).

Step 4: Synthesis of (2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methanol

To a solution of ethyl

- 5 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylpyrazolo[1,5-*a*]pyridine-3-carboxylate (5.10 g, 14.6 mmol) in H₂O (15 mL) was added H₂SO₄ (15 mL). The mixture was stirred at 80 °C for 18 hrs. The reaction was adjusted pH=7~8 with 15% aq. NaOH solution at 0 °C. The resulting mixture was diluted with EtOAc (30 mL) and washed with water (30 mL). After partition, the aqueous layer was extracted with EtOAc (30 mL x 2). The combined
10 organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethylacetate/Petroleum ether gradient @ 40 mL/min). Compound (2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methanol (1.90 g, 80.1% yield) was obtained as a yellow solid. $R_f = 0.3$ (Petroleum ether: Ethyl acetate =
15 1:1). ¹H NMR (400 MHz, CDCl₃) δ 8.30 (d, $J = 7.2$ Hz, 1H), 7.37 (s, 1H), 6.63 (d, $J = 7.2$ Hz, 1H), 6.24 (s, 1H), 4.69 (s, 2H), 2.47 (s, 3H).

Step 5: Synthesis of 2-methylpyrazolo[1,5-*a*]pyridine-5-carbaldehyde

- To a solution of (2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methanol (900 mg, 5.55 mmol) in DCM (10 mL) was added MnO₂ (2.41 g, 27.75 mmol). The mixture was stirred at 25 °C
20 for 16 hrs. The mixture was filtered through a pad of celite and concentrated under reduced pressure.

The crude product 2-methylpyrazolo[1,5-*a*]pyridine-5-carbaldehyde (770 mg, crude) was obtained as yellow solid, which was used into the next step without further purification. $R_f = 0.66$ (Petroleum ether: Ethyl acetate = 1: 1)

- 25 **Step 6: Synthesis of *tert*-butyl**

(*S*)-2-methyl-4-((2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)piperazine-1-carboxylate

- To a solution of 2-methylpyrazolo[1,5-*a*]pyridine-5-carbaldehyde (770 mg, 4.81 mmol) and *tert*-butyl (2*S*)-2-methylpiperazine-1-carboxylate (963 mg, 4.81 mmol) in
30 MeOH (10 mL) was added AcOH (289 mg, 4.81 mmol). The mixture was stirred at 50 °C for 6 hrs. The reaction mixture was cooled to 25 °C, and NaBH₃CN (604.18 mg, 9.61 mmol, 2 eq) was added. The mixture was stirred at 25 °C for 16 hrs. The mixture was

concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethylacetate/Petroleum ether gradient @ 30 mL/min). Compound *tert*-butyl (*S*)-2-methyl-4-((2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)piperazine-1-carboxylate (1.10 g, 46.5% yield, 70% purity) was obtained as a colorless oil. LCMS (ESI⁺): *m/z* 345.6 [M+H]⁺.

Step 7: Synthesis of *tert*-butyl

(*S*)-4-((3-iodo-2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of *tert*-butyl (*S*)-2-methyl-4-((2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)piperazine-1-carboxylate (1.10 g, 3.19 mmol) in MeCN (10 mL) was added NIS (718 mg, 3.19 mmol). The mixture was stirred at 25 °C for 2 hrs. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethylacetate/Petroleum ether gradient @ 30 mL/min). Compound *tert*-butyl (*S*)-4-((3-iodo-2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (1.40 g, 93.2% yield) was obtained as a light yellow solid. *R*_f = 0.24 (Petroleum ether: Ethyl acetate = 5:1). ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, *J* = 7.2 Hz, 1H), 7.24 (s, 1H), 6.81 (d, *J* = 6.8 Hz, 1H), 4.21 (s, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.60 - 3.52 (m, 1H), 3.41 (d, *J* = 13.8 Hz, 1H), 3.20 - 3.09 (m, 1H), 2.77 (d, *J* = 10.8 Hz, 1H), 2.59 (d, *J* = 11.2 Hz, 1H), 2.46 (s, 3H), 2.22 - 2.15 (m, 1H), 2.14 - 2.05 (m, 1H), 1.46 (s, 9H), 1.27 (d, *J* = 6.8 Hz, 3H).

Step 8: Synthesis of *tert*-butyl

(*S*)-4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of 3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (149 mg, 638 μmol) and *tert*-butyl (*S*)-4-((3-iodo-2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (300 mg, 638 μmol) in dioxane (4 mL) were added CuI (24.3 mg, 126 μmol), trans-1,2-Diaminocyclohexane (14.6 mg, 128 μmol) and Cs₂CO₃ (416 mg, 1.28 mmol). The mixture was stirred at 95 °C for 8 hrs under microwave. The mixture was filtered and

concentrated under reduced pressure to afford the crude product, which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethylacetate/Petroleum ether gradient @ 25 mL/min). Compound *tert*-butyl (S)-4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (149 mg, 22.7% yield, 56% purity) was obtained as a yellow solid. R_f = 0.25 (Petroleum ether: Ethyl acetate = 1:1). LCMS (ESI⁺): m/z 577.5 [M+H]⁺.

Step 9: Synthesis of

(S)-3-(4-methoxybenzyl)-1-(2-methyl-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

A mixture of *tert*-butyl (S)-4-((3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-2-methylpyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (149 mg, 258 μmol) and HCl/dioxane (4 M, 3 mL) was stirred at 25 °C for 2 hrs. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (Column:Kromasil 100-5-C18 30*150 mm, Mobile Phase A: water (0.01% FA), Mobile Phase B: acetonitrile, 25 mL/min, gradient condition from 5% B to 45%). Compound (S)-3-(4-methoxybenzyl)-1-(2-methyl-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (44.0 mg, 24.6% yield, 74% purity, HCl) was obtained as a colorless oil. LCMS (ESI⁺): m/z 477.5 [M+H]⁺.

Step 10: Synthesis of

(S)-1-(5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)-2-methylpyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

To a solution of (S)-3-(4-methoxybenzyl)-1-(2-methyl-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (44.0 mg, 85.8 μmol, HCl) in MeOH (2 mL) was added TEA (17.4 mg, 172 μmol) and the mixture was stirred at 25 °C for 30 min. Then 2-methylpropanal (12.4 mg, 172 μmol) and AcOH (18.0 mg, 300 μmol) were added. The mixture was stirred at 50 °C for 2 hrs. The reaction mixture was cooled to 25 °C and NaBH₃CN (10.8 mg, 172 μmol) was added. The mixture was stirred at 25 °C for 2 hrs. The mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM: MeOH = 10: 1, R_f = 0.7). Compound

(*S*)-1-(5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)-2-methylpyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (34.0 mg, 58.8% yield, 79% purity) was obtained as a colorless oil. $R_f = 0.7$ (Dichloromethane: Methanol = 10: 1). LCMS (ESI⁺): m/z 533.8 [M+H]⁺.

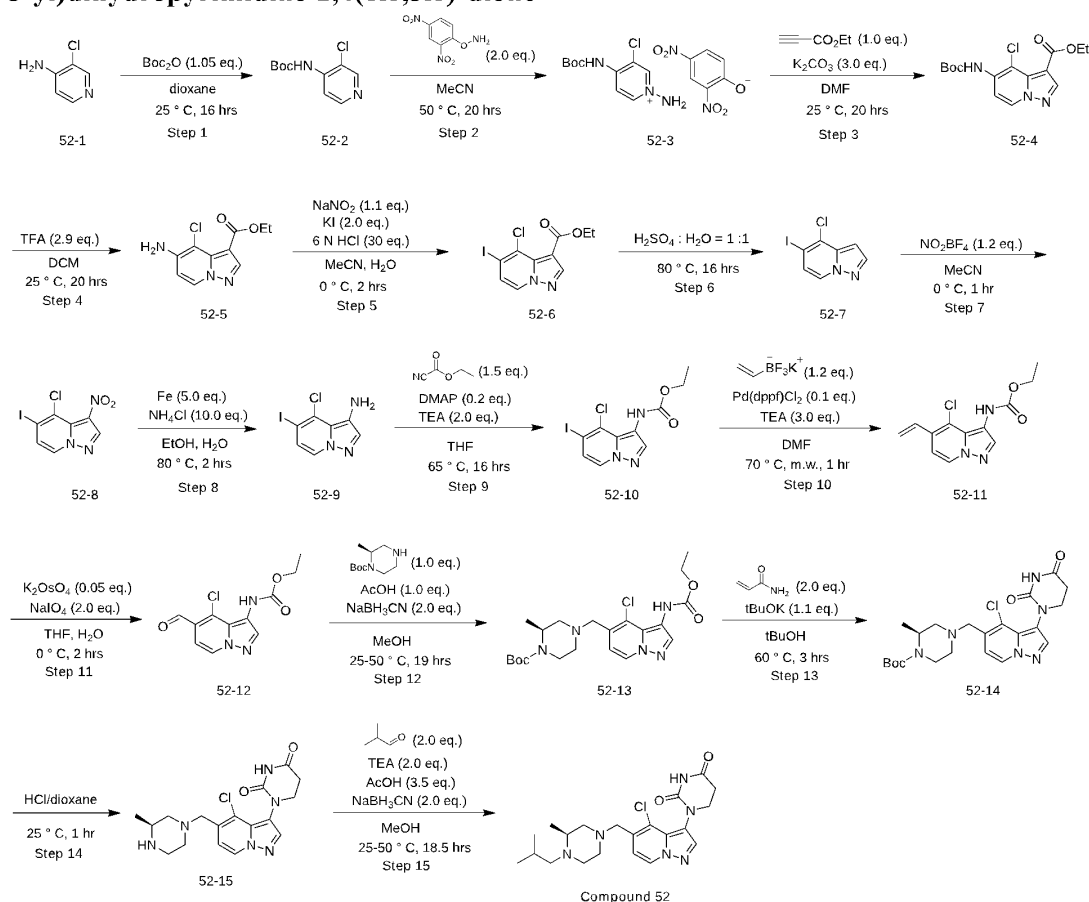
5 Step 11: Synthesis of compound 51

(*S*)-1-(5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)-2-methylpyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

To a solution of

(*S*)-1-(5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)-2-methylpyrazolo[1,5-*a*]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (34.0 mg, 63.8 μ mol) in TFA (0.5 mL) was added TfOH (848 mg, 5.65 mmol, 0.5 mL). The mixture was stirred at 25 °C for 2 hrs. The mixture was adjusted pH=7~8 with aq. NaHCO₃ solution. The resulting mixture was diluted with water (20 mL). After partition, the aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (Column: Kromasil 100-5-C18 30x150 mm, Mobile Phase A: water (0.01% FA), Mobile Phase B: acetonitrile, 25 mL/min, gradient condition from 1% B to 40%). Compound (*S*)-1-(5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)-2-methylpyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (7.53 mg, 26.0% yield, 91.0% purity) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.43 (br. s., 1H), 8.50 (d, $J = 6.8$ Hz, 1H), 7.48 - 7.33 (m, 1H), 6.89 - 6.76 (m, 1H), 3.71 - 3.67 (m, 2H), 3.54 - 3.53 (m, 2H), 2.88 - 2.76 (m, 3H), 2.75 - 2.63 (m, 3H), 2.61 - 2.54 (m, 2H), 2.45 - 2.30 (m, 2H), 2.27 (s, 3H), 2.23 - 2.11 (m, 1H), 2.04 - 1.78 (m, 1H), 1.18 - 1.01 (m, 3H), 0.96 - 0.83 (m, 6H). LCMS (ESI⁺): m/z 413.3 [M+H]⁺.

25

Example 19: Preparation of compound 52:**(S)-1-(4-chloro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione****5 Step 1: Synthesis of *tert*-butyl (3-chloropyridin-4-yl)carbamate**

To a solution of 3-chloropyridin-4-amine (25.0 g, 195 mmol) in dioxane (80 mL) was added Boc_2O (44.6 g, 204 mmol, 46.9 mL). The mixture was stirred at 25 °C for 16 hrs. The mixture was concentrated under reduced pressure to give *tert*-butyl (3-chloropyridin-4-yl)carbamate (45 g, crude) as a yellow solid, which was used into the next step without further purification. LCMS (ESI^+): m/z 173.4 [$\text{M}+\text{H}-56$] $^+$.

Step 2: Synthesis of *tert*-butyl***N*-(1-amino-3-chloro-pyridin-1-ium-4-yl)carbamate;2,4-dinitrophenolate**

To a solution of *tert*-butyl (3-chloropyridin-4-yl)carbamate (45.0 g, 197 mmol) in MeCN (300 mL) was added O-(2,4-dinitrophenyl)hydroxylamine (78.4 g, 394 mmol). The mixture was stirred at 50 °C for 20 hrs. The mixture was concentrated under reduced

pressure to give *tert*-butyl

N-(1-amino-3-chloro-pyridin-1-ium-4-yl)carbamate;2,4-dinitrophenolate (84 g, crude) as a brown oil, which was used into the next step without further purification. $R_f = 0.07$

(**Petroleum ether: Ethyl acetate** = 10: 1).

5 Step 3: Synthesis of ethyl

5-((*tert*-butoxycarbonyl)amino)-4-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate

To a solution of *tert*-butyl

N-(1-amino-3-chloro-pyridin-1-ium-4-yl)carbamate;2,4-dinitrophenolate (84.0 g, 196 mmol) in DMF (450 mL) were added K_2CO_3 (81.3 g, 588 mmol) and ethyl propiolate (19.3 g, 196 mmol, 19.3 mL). The mixture was stirred at 25 °C for 20 hrs. The mixture was diluted with EtOAc (500 mL) and washed with brine (500 mL x 3). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethylacetate/Petroleum ether gradient @ 70 mL/min) to give ethyl 5-((*tert*-butoxycarbonyl)amino)-4-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate (31.8 g, 37.7% yield) as a yellow solid. $R_f = 0.58$ (**Petroleum ether: Ethyl acetate** = 3: 1). LCMS (ESI⁺): m/z 340.3 [M+H]⁺.

Step 4: Synthesis of ethyl 5-amino-4-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate

To a solution of ethyl

5-((*tert*-butoxycarbonyl)amino)-4-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate (31.8 g, 93.6 mmol) (a mixture of ethyl 5-((*tert*-butoxycarbonyl)amino)-6-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate) in DCM (50 mL) was added TFA (30.7 g, 269.3 mmol, 20 mL). The mixture was stirred at 25 °C for 20 hrs. The mixture was concentrated to remove solvent and then adjusted pH=7~8 with aq. $NaHCO_3$ solution. The resulting mixture was diluted with EtOAc (200 mL) and washed with water (200 mL). After partition, the aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethylacetate/Petroleum ether gradient @ 60 mL/min) to give ethyl 5-amino-6-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate (4.63 g, 20.6% yield) as a yellow

solid and ethyl 5-amino-4-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate (5.8 g, 25.9% yield) as a yellow solid. $R_f = 0.2$ (Petroleum ether: Ethyl acetate = 3: 1). LCMS (ESI⁺): m/z 240.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 8.23 (s, 1H), 7.31 (s, 1H), 4.75 - 4.46 (m, 2H), 4.34 (q, $J = 7.2$ Hz, 2H), 1.39 (t, $J = 7.2$ Hz, 3H)

5 Step 5: Synthesis of ethyl 4-chloro-5-iodopyrazolo[1,5-*a*]pyridine-3-carboxylate

To a solution of ethyl 5-amino-4-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate (2.00 g, 8.35 mmol) in MeCN (14 mL) and HCl (6 M, 41.7 mL) was added dropwise a solution of NaNO₂ (633.4 mg, 9.18 mmol) in H₂O (7 mL). The mixture was stirred at 0 °C for 1 hr. A solution of KI (2.77 g, 16.7 mmol) in H₂O (7 mL) was added dropwise into the mixture.

- 10 The reaction was stirred at 0 °C for 1 hr. The reaction was adjusted pH=7~8 with 15% aq. NaOH solution. The resulting mixture was diluted with EtOAc (30 mL) and washed with water (30 mL). After partition, the aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethylacetate/Petroleum ether gradient @ 40 mL/min) to give ethyl 4-chloro-5-iodopyrazolo[1,5-*a*]pyridine-3-carboxylate (2.2 g, 72.2% yield) as a yellow solid. $R_f = 0.6$ (Petroleum ether: Ethyl acetate = 5: 1). LCMS (ESI⁺): m/z 351.1 [M+H]⁺.

Step 6: Synthesis of 4-chloro-5-iodopyrazolo[1,5-*a*]pyridine

- 20 To a solution of ethyl 4-chloro-5-iodopyrazolo[1,5-*a*]pyridine-3-carboxylate (2.20 g, 6.28 mmol) in H₂O (5 mL) was added H₂SO₄ (9.20 g, 93.8 mmol, 5 mL). The mixture was stirred at 80 °C for 16 hrs. The reaction was adjusted pH=7~8 with 15% aq. NaOH solution at 0 °C. The resulting mixture was diluted with EtOAc (30 mL) and washed with water (30 mL). After partition, the aqueous layer was extracted with EtOAc (30 mL X 2).
- 25 The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give 4-chloro-5-iodopyrazolo[1,5-*a*]pyridine (1.5 g, crude) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.12 (dd, $J = 0.8, 7.2$ Hz, 1H), 7.93 (d, $J = 2.0$ Hz, 1H), 7.08 (d, $J = 7.2$ Hz, 1H), 6.65 (dd, $J = 0.8, 2.0$ Hz, 1H).

Step 7: Synthesis of 4-chloro-5-iodo-3-nitropyrazolo[1,5-*a*]pyridine

- 30 To a solution of 4-chloro-5-iodopyrazolo[1,5-*a*]pyridine (300 mg, 1.08 mmol) in MeCN (3 mL) was added nitronium-tetrafluoroborate (171.7 mg, 1.29 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hr. The reaction mixture was quenched by addition ice

water (20 mL). Lots of precipitates was formed and collected solids through filtration. The crude product was dried in vacuum to give 4-chloro-5-iodo-3-nitropyrzolo[1,5-*a*]pyridine (160 mg, crude) as a dark green solid. LCMS (ESI⁺): *m/z* 324.1 [M+H]⁺.

Step 8: Synthesis of 4-chloro-5-iodopyrazolo[1,5-*a*]pyridin-3-amine

5 To a solution of 4-chloro-5-iodo-3-nitropyrzolo[1,5-*a*]pyridine (160 mg, 495 μmol) in EtOH (4 mL) and H₂O (1 mL) were added Fe (138 mg, 2.47 mmol) and NH₄Cl (265 mg, 4.95 mmol). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was concentrated to remove solvent. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with EtOAc (20 mL x
10 2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (Condition: 30% to 60% of phase B (Phase A: water (neutral), Phase B: MeCN, Flow rate: 25 mL/min) to give 4-chloro-5-iodopyrazolo[1,5-*a*]pyridin-3-amine (100 mg, 68.2% yield) as a yellow solid. LCMS (ESI⁺): *m/z* 294.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 7.2 Hz, 1H), 7.58 (s, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 3.88 - 3.26 (m, 2H)
15

Step 9: Synthesis of ethyl (4-chloro-5-iodopyrazolo[1,5-*a*]pyridin-3-yl)carbamate

To a solution of 4-chloro-5-iodopyrazolo[1,5-*a*]pyridin-3-amine (430 mg, 1.47 mmol) in THF (5 mL) were added DMAP (35.8 mg, 293 μmol) and TEA (297 mg, 2.93 mmol, 408 μL). Then ethyl cyanoformate (218 mg, 2.20 mmol) was added. The mixture was
20 stirred at 65 °C for 16 hrs. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethylacetate/Petroleum ether gradient @ 30 mL/min) to give ethyl (4-chloro-5-iodopyrazolo[1,5-*a*]pyridin-3-yl)carbamate (459 mg, 80.6% yield) as a green solid. LCMS (ESI⁺): *m/z* 366.2 [M+H]⁺.

25 **Step 10: Synthesis of ethyl (4-chloro-5-vinylpyrazolo[1,5-*a*]pyridin-3-yl)carbamate**

To a solution of potassium trifluoro(vinyl)borate (170 mg, 1.27 mmol) and ethyl (4-chloro-5-iodopyrazolo[1,5-*a*]pyridin-3-yl)carbamate (387 mg, 1.06 mmol) in DMF (4 mL) were added Pd(dppf)Cl₂ (77.5 mg, 106 μmol) and TEA (321 mg, 3.18 mmol, 442 μL). The mixture was stirred at 70 °C for 1 hr under microwave. The mixture was diluted with
30 EtOAc (20 mL) and washed with brine (20 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (Condition: 70% to 100% of phase B (Phase A: water (neutral), Phase B: MeCN, Flow rate: 25 mL/min) to give ethyl (4-chloro-5-vinylpyrazolo[1,5-*a*]pyridin-3-yl)carbamate (280 mg, 52.8% yield) as a

yellow solid. LCMS (ESI⁺): m/z 266.3 [M+H]⁺.

Step 11: Synthesis of ethyl (4-chloro-5-formylpyrazolo[1,5-*a*]pyridin-3-yl)carbamate

To a solution of ethyl (4-chloro-5-vinylpyrazolo[1,5-*a*]pyridin-3-yl)carbamate (280 mg, 1.05 mmol) in THF (3 mL) was added potassium osmate(VI) dihydrate (19.4 mg, 52.7 μmol) at 0 °C, then a solution of NaIO₄ (451 mg, 2.11 mmol, 116.8 μL) in H₂O (1 mL) was added. The mixture was stirred at 0 °C for 2 hrs. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). After partition, the aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethylacetate/Petroleum ether gradient @ 20 mL/min) to give ethyl (4-chloro-5-formylpyrazolo[1,5-*a*]pyridin-3-yl)carbamate (180 mg, 38.3% yield) as a yellow solid. R_f = 0.35 (Petroleum ether: Ethyl acetate = 4: 1). LCMS (ESI⁺): m/z 268.0 [M+H]⁺.

Step 12: Synthesis of *tert*-butyl

(*S*)-4-((4-chloro-3-((ethoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of ethyl (4-chloro-5-formylpyrazolo[1,5-*a*]pyridin-3-yl)carbamate (180 mg, 673 μmol) and *tert*-butyl (*S*)-2-methylpiperazine-1-carboxylate (135 mg, 673 μmol) in MeOH (3 mL) was added AcOH (40.4 mg, 673 μmol, 38.5 μL). The mixture was stirred at 50 °C for 16 hrs. The reaction mixture was cooled to 25 °C, and NaBH₃CN (84.5 mg, 1.34 mmol) was added. The mixture was stirred at 25 °C for 3 hrs. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethylacetate/Petroleum ether gradient @ 20 mL/min) to give *tert*-butyl (*S*)-4-((4-chloro-3-((ethoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (130 mg, 27.8% yield) as a white solid. R_f = 0.3 (Petroleum ether: Ethyl acetate = 3: 1). LCMS (ESI⁺): m/z 474.4 [M+Na]⁺.

Step 13: Synthesis of *tert*-butyl

(*S*)-4-((4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate

To a solution of acrylamide (15.7 mg, 221.3 μmol) and *tert*-butyl (*S*)-4-((4-chloro-3-((ethoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (50 mg, 110.6 μmol) in *t*-BuOH (1 mL) was added *t*-BuOK (1 M, 121.7 μL). The mixture was stirred at 60 °C for 3 hrs. The mixture was concentrated under

reduced pressure. The residue was purified by prep-TLC to give *tert*-butyl (*S*)-4-((4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (35 mg, 49.8% yield) as a colorless oil. R_f = 0.7 (Petroleum ether: Ethyl acetate = 1: 2). LCMS (ESI⁺): m/z 499.5 [M+Na]⁺.

5 **Step 14: Synthesis of**

(*S*)-1-(4-chloro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

A mixture of *tert*-butyl

(*S*)-4-((4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyridin-5-yl)methyl)-2-methylpiperazine-1-carboxylate (35.0 mg, 73.4 μ mol) and HCl/dioxane (4 M, 1
10 mL) was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to give

(*S*)-1-(4-chloro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (30 mg, crude, HCl) as a light yellow oil, which was used into
15 the next step without further purification. LCMS (ESI⁺): m/z 377.4 [M+H]⁺.

Step 15: Synthesis of

(*S*)-1-(4-chloro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

To a solution of

(*S*)-1-(4-chloro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (30.0 mg, 72.6 μ mol, HCl) in MeOH (1 mL) was added Et₃N (14.7 mg, 145 μ mol, 20.2 μ L) and the mixture was stirred at 25 °C for 30 min. Then isobutyraldehyde (10.5 mg, 145 μ mol, 13.3 μ L) and AcOH (15.3 mg, 254 μ mol, 14.5 μ L) were added. The mixture was stirred at 50 °C for 2 hrs. The reaction mixture was cooled to
25 25 °C, and NaBH₃CN (9.12 mg, 145.2 μ mol) was added. The mixture was stirred at 25 °C for 16 hr. The mixture was concentrated under reduced pressure. The residues was purified by prep-HPLC (Column: Kromasil 100-5-C18 30*150 mm, Mobile Phase A: water (0.01% FA), Mobile Phase B: acetonitrile, 25 mL/min, gradient condition from 1% B to 40%) to give

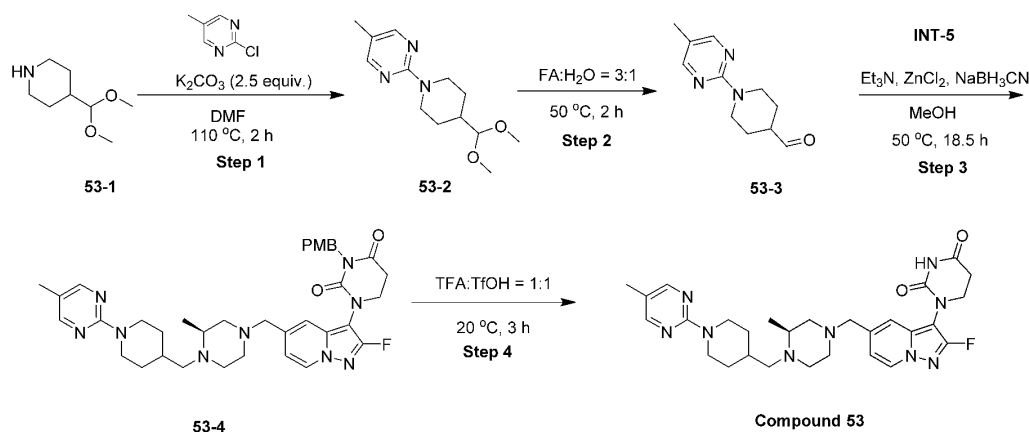
(*S*)-1-(4-chloro-5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (5.24 mg, 16.7% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1H), 8.65 (d, J = 7.2 Hz, 1H), 8.11 (s, 1H), 7.05 (d, J = 7.2 Hz, 1H), 3.73 - 3.67 (m, 2H), 3.59 (s, 2H), 2.80 - 2.73 (m, 3H), 2.64 - 2.56 (m, 2H), 2.37 - 2.24 (m, 3H), 2.17 - 2.08 (m, 1H), 2.05 - 1.95 (m, 1H), 1.89 - 1.81 (m, 1H), 1.74 -
35 1.64 (m, 1H), 0.94 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.4 Hz, 6H). LCMS (ESI⁺): m/z 433.3

$[M+H]^+$.

Example 19: Preparation of compound 53:

(S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-methylpyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

5 Step 1: Synthesis of 2-(4-(dimethoxymethyl)piperidin-1-yl)-5-methylpyrimidine



To a solution of 4-(dimethoxymethyl)piperidine (520 mg, 3.25 mmol) in DMF (10 mL) were added K_2CO_3 (540 mg, 3.89 mmol) and 2-chloro-5-methylpyrimidine (500 mg, 3.89 mmol). The mixture was stirred at 110 °C for 2 hrs. The reaction was quenched by water and extracted by DCM (2 x 20 mL), the organic phase was washed by brine and dried over Na_2SO_4 . The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 35mL/min) to give 2-(4-(dimethoxymethyl)piperidin-1-yl)-5-methylpyrimidine (300 mg, 37% yield) as a white solid. R_f = 0.5 (Ethyl acetate/Petroleum ether = 5: 1). LCMS (ESI⁺): m/z 252.5 $[M+H]^+$.

Step 2: Synthesis of 1-(5-methylpyrimidin-2-yl)piperidine-4-carbaldehyde

To a solution of 2-(4-(dimethoxymethyl)piperidin-1-yl)-5-methylpyrimidine (300 mg, 1.2 mmol) in H_2O (0.5 mL) was added FA (1.5 mL). The mixture was stirred at 50 °C for 2 hrs. The mixture was concentrated under reduced pressure to give 1-(5-methylpyrimidin-2-yl)piperidine-4-carbaldehyde (300 mg, crude) as a light yellow solid, which was used for next step without purified. LCMS (ESI⁺): m/z 220.4 $[M+H_2O]^+$.

Step 3: Synthesis of

(S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-methylpyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

To a solution of

(S)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (100 mg, 0.20 mmol, HCl) in MeOH (2 mL) was added TEA (34.9 mg, 0.35 mmol) and the mixture was stirred at 20 °C for 30 min.

- 5 Then 1-(5-methylpyrimidin-2-yl)piperidine-4-carbaldehyde (100 mg, 0.49 mmol) and ZnCl₂ (0.5 mL, 1 mmol, 2 M in THF) was added. The mixture was stirred at 50 °C for 16 hrs. The reaction mixture was cooled to 20 °C, and NaBH₃CN (21.7 mg, 0.35 mmol) was added. The mixture was stirred at 20 °C for 2 hrs. The mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM: MeOH = 10: 1) to give
- 10 (S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-methylpyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (65 mg, 49% yield, 80% purity) as a light yellow oil. R_f = 0.4 (Dichloromethane: Methanol = 10: 1). LCMS (ESI⁺): m/z 670.8 [M+H]⁺.

Step 4:

- 15 **(S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-methylpyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione**

To a solution of

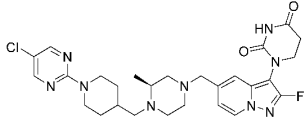
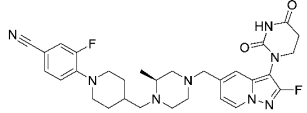
- (S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-methylpyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (65.0 mg, 0.10 mmol) in TFA (1 mL) was added TfOH (1 mL). The mixture was stirred at 20 °C for 3 hrs. The mixture was adjusted pH=7~8 with aq. NaHCO₃ solution. The resulting mixture was diluted with ethyl acetate (15 mL) and washed with brine (15 mL). After partition, the aqueous layer was extracted with ethyl acetate (15 mLx2). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and
- 25 concentrated in vacuo. The crude product was purified by reversed-phase HPLC (Condition: 40% to 60% of phase B (Phase A: water (neutral), Phase B: MeCN, Flow rate: 20 mL/min) to give

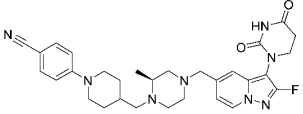
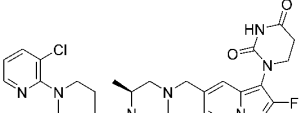
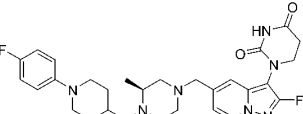
- (S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-methylpyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (36 mg, 58% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.54 (s, 1H), 8.51 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.48 (s, 1H), 7.39 (d, *J* = 11.9 Hz, 1H), 6.96 (d, *J* = 5.5 Hz, 1H), 3.92 (s, 4H), 3.74 (t, *J* = 6.6 Hz, 3H), 3.59 – 3.42 (m, 2H), 3.03 – 2.71 (m, 4H), 2.63 (d, *J* = 35.0 Hz, 3H), 2.41 – 2.15 (m, 3H), 2.07 – 1.60 (m, 5H), 1.24 (s, 3H), 0.94 (d, *J* = 6.1 Hz, 4H). LCMS (ESI⁺): m/z 550.31 [M+H]⁺.
- 30

Example 20: The compounds in **Table 7** were prepared by the method of **compound 53**

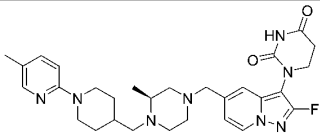
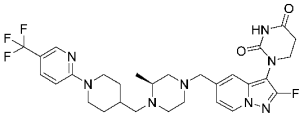
Table 7

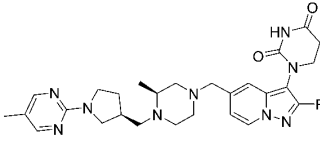
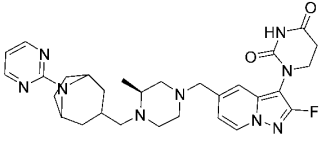
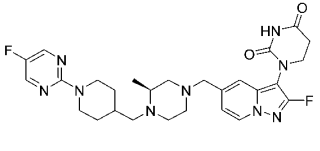
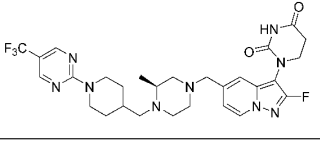
No.	Structure	Compound name and characterization
54		(<i>S</i>)-1-(2-fluoro-5-((3-methyl-4-((1-(pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5- <i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (br. s., 1H), 8.51 (d, <i>J</i> = 7.2 Hz, 1H), 8.31 (d, <i>J</i> = 4.8 Hz, 2H), 7.53 - 7.45 (m, 1H), 7.00 - 6.93 (m, 1H), 6.58 - 6.52 (m, 1H), 4.67 - 4.58 (m, 2H), 3.74 (t, <i>J</i> = 6.8 Hz, 2H), 3.55 - 3.52 (m, 2H), 2.89 - 2.76 (m, 5H), 2.62 - 2.54 (m, 2H), 2.48 - 2.43 (m, 1H), 2.38 - 2.31 (m, 1H), 2.25 - 2.15 (m, 2H), 1.98 - 1.89 (m, 2H), 1.86 - 1.79 (m, 1H), 1.79 - 1.70 (m, 1H), 1.68 - 1.61 (m, 1H), 1.08 - 0.85 (m, 5H); LCMS (ESI ⁺): <i>m/z</i> 536.5 [M+H] ⁺ .
55		(<i>S</i>)-1-(5-((4-((1-(5-chloropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5- <i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (br. s., 1H), 8.51 (d, <i>J</i> = 7.2 Hz, 1H), 8.07 (d, <i>J</i> = 2.4 Hz, 1H), 7.54 (dd, <i>J</i> = 2.4, 9.2 Hz, 1H), 7.49 (s, 1H), 7.01 - 6.93 (m, 1H), 6.84 (d, <i>J</i> = 9.2 Hz, 1H), 4.27 - 4.18 (m, 2H), 3.77 - 3.72 (m, 2H), 3.49 - 3.48 (m, 2H), 2.84 - 2.74 (m, 5H), 2.66 - 2.56 (m, 2H), 2.46 - 2.30 (m, 2H), 2.27 - 2.15 (m, 2H), 2.02 - 1.90 (m, 2H), 1.86 - 1.77 (m, 1H), 1.75 - 1.61 (m, 2H), 1.13 - 0.90 (m, 5H); LCMS (ESI ⁺): <i>m/z</i> 569.2 [M+H] ⁺ .
56		(<i>S</i>)-6-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2 <i>H</i>)-yl)-2-fluoropyrazolo[1,5- <i>a</i>]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)nicotinonitrile

		nonitrile; ^1H NMR (400 MHz, DMSO- d_6) δ 10.57 (s, 1H), 8.51 (d, $J = 7.2$ Hz, 1H), 8.44 (d, $J = 2.4$ Hz, 1H), 7.79 (dd, $J = 2.4, 9.2$ Hz, 1H), 7.49 (s, 1H), 6.99 - 6.94 (m, 1H), 6.90 (d, $J = 9.2$ Hz, 1H), 4.47 - 4.35 (m, 2H), 3.74 (t, $J = 6.8$ Hz, 2H), 3.53 - 3.51 (m, 2H), 2.97 - 2.87 (m, 2H), 2.83 - 2.76 (m, 3H), 2.64 - 2.55 (m, 2H), 2.48 - 2.40 (m, 2H), 2.24 - 2.13 (m, 2H), 1.99 - 1.88 (m, 2H), 1.87 - 1.75 (m, 2H), 1.72 - 1.64 (m, 1H), 1.10 - 0.95 (m, 2H), 0.92 (d, $J = 6.0$ Hz, 3H); LCMS (ESI $^+$): m/z 560.4 [M+H] $^+$.
57		(S)-1-(5-((4-((1-(5-chloropyrimidin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO- d_6) δ 10.57 (br. s., 1H), 8.54 (d, $J = 7.2$ Hz, 1H), 8.39 (s, 2H), 7.52 (s, 1H), 6.97 (d, $J = 6.8$ Hz, 1H), 4.63 - 4.53 (m, 2H), 3.75 (t, $J = 6.8$ Hz, 2H), 3.56 - 3.54 (m, 2H), 2.97 - 2.85 (m, 3H), 2.83 - 2.63 (m, 6H), 2.57 - 2.53 (m, 1H), 2.46 - 2.38 (m, 1H), 2.24 - 2.09 (m, 1H), 1.94 - 1.83 (m, 2H), 1.74 - 1.66 (m, 1H), 1.27 - 1.21 (m, 1H), 1.15 - 0.97 (m, 5H); LCMS (ESI $^+$): m/z 570.2 [M+H] $^+$.
58		(S)-4-(4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)-3-fluorobenzonitrile; ^1H NMR (400 MHz, DMSO- d_6) δ 10.56 (s, 1H), 8.51 (d, $J = 7.2$ Hz, 1H), 7.70 - 7.61 (m, 1H), 7.53 (dd, $J = 1.2, 8.4$ Hz, 1H), 7.49 (s, 1H), 7.14 - 7.07 (m, 1H), 6.99 - 6.93 (m, 1H), 3.74 (t, $J = 6.8$ Hz, 2H), 3.56 - 3.51 (m, 2H), 3.47 - 3.46 (m, 2H), 2.85 - 2.71 (m, 5H), 2.69 - 2.53 (m, 3H), 2.42 - 2.30 (m, 1H), 2.27 - 2.12 (m, 2H), 2.01 - 1.81 (m, 3H), 1.75 - 1.58 (m, 2H), 1.27 - 1.11 (m, 2H), 0.94

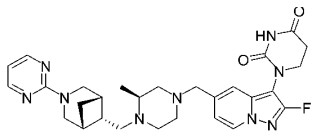
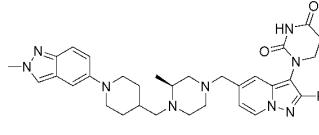
		(d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 577.3 [M+H] ⁺ .
59		(S)-4-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)benzonitrile; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.57 (br. s., 1H), 8.53 (d, $J = 7.2$ Hz, 1H), 7.57 - 7.49 (m, 3H), 7.01 - 6.94 (m, 3H), 4.00 - 3.85 (m, 3H), 3.77 - 3.73 (m, 2H), 3.52 - 3.50 (m, 2H), 2.91 - 2.77 (m, 6H), 2.70 - 2.57 (m, 4H), 2.36 - 2.24 (m, 2H), 1.89 - 1.77 (m, 2H), 1.72 - 1.64 (m, 1H), 1.19 - 0.97 (m, 5H); LCMS (ESI ⁺): m/z 559.2 [M+H] ⁺ .
60		(S)-1-(5-((4-((1-(3-chloropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (s, 1H), 8.51 (d, $J = 7.2$ Hz, 1H), 8.18 (dd, $J = 1.2, 4.8$ Hz, 1H), 7.76 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.49 (s, 1H), 7.01 - 6.92 (m, 2H), 3.74 (t, $J = 6.8$ Hz, 2H), 3.71 - 3.65 (m, 2H), 3.48 - 3.46 (m, 2H), 2.82 - 2.66 (m, 5H), 2.65 - 2.52 (m, 3H), 2.41 - 2.30 (m, 1H), 2.25 - 2.12 (m, 2H), 2.02 - 1.81 (m, 3H), 1.74 - 1.57 (m, 2H), 1.28 - 1.13 (m, 2H), 0.95 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 569.2 [M+H] ⁺ .
61		(S)-1-(2-fluoro-5-((4-((1-(4-fluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (s, 1H), 8.51 (d, $J = 7.2$ Hz, 1H), 7.49 (s, 1H), 7.04 - 6.89 (m, 5H), 3.74 (t, $J = 6.8$ Hz, 2H), 3.49 - 3.45 (m, 4H), 2.88 - 2.76 (m, 3H), 2.67 - 2.52 (m, 5H), 2.47 - 2.35 (m, 1H), 2.27 - 2.17 (m, 2H), 2.07 - 1.90 (m, 2H), 1.89 - 1.79 (m, 1H), 1.72 - 1.64 (m, 1H),

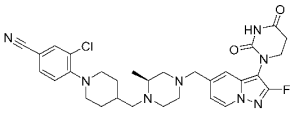
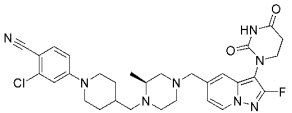
		1.63 - 1.50 (m, 1H), 1.28 - 1.08 (m, 2H), 0.96 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 552.4 [M+H] ⁺ .
62		(<i>S</i>)-1-(5-((4-((1-(2,4-difluorophenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5- <i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.55 (s, 1H), 8.50 (d, $J = 7.2$ Hz, 1H), 7.48 (s, 1H), 7.19 - 7.10 (m, 1H), 7.09 - 7.01 (m, 1H), 6.99 - 6.92 (m, 2H), 3.74 (t, $J = 6.8$ Hz, 2H), 3.48 - 3.46 (m, 2H), 3.26 - 3.19 (m, 2H), 2.79 (t, $J = 6.8$ Hz, 2H), 2.66 - 2.52 (m, 5H), 2.41 - 2.30 (m, 2H), 2.26 - 2.12 (m, 2H), 2.02 - 1.90 (m, 2H), 1.88 - 1.81 (m, 1H), 1.73 - 1.65 (m, 1H), 1.61 - 1.48 (m, 1H), 1.30 - 1.15 (m, 2H), 0.95 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 570.3 [M+H] ⁺ .
63		(<i>S</i>)-1-(2-fluoro-5-((4-((1-(3-fluoropyridin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5- <i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (br. s., 1H), 8.51 (d, $J = 7.2$ Hz, 1H), 7.98 (d, $J = 4.8$ Hz, 1H), 7.50 - 7.42 (m, 2H), 6.96 (dd, $J = 1.6, 7.2$ Hz, 1H), 6.86 - 6.79 (m, 1H), 3.92 (d, $J = 12.0$ Hz, 2H), 3.74 (t, $J = 6.8$ Hz, 2H), 3.49 - 3.46 (m, 2H), 2.86 - 2.74 (m, 5H), 2.64 - 2.52 (m, 3H), 2.40 - 2.30 (m, 1H), 2.25 - 2.13 (m, 2H), 1.99 - 1.89 (m, 2H), 1.88 - 1.79 (m, 1H), 1.72 - 1.62 (m, 2H), 1.26 - 1.08 (m, 2H), 0.94 (d, $J = 6.0$ Hz, 3H); LCMS (ESI ⁺): m/z 553.3 [M+H] ⁺ .
64		(<i>S</i>)-5-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2 <i>H</i>)-yl)-2-fluoropyrazolo[1,5- <i>a</i>]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)picolinonitrile; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.55

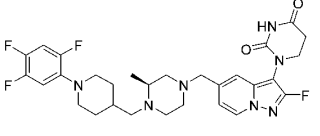
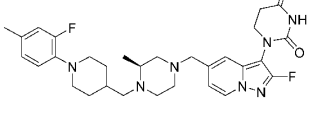
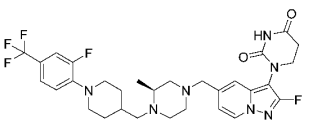
		(s, 1H), 8.56 - 8.45 (m, 1H), 8.40 - 8.38 (m, 1H), 7.74 - 7.63 (m, 1H), 7.48 (s, 1H), 7.35 - 7.24 (m, 1H), 7.00 - 6.90 (m, 1H), 4.08 - 3.91 (m, 2H), 3.77 - 3.69 (m, 2H), 3.51 - 3.46 (m, 2H), 2.96 - 2.83 (m, 3H), 2.82 - 2.74 (m, 3H), 2.62 - 2.53 (m, 2H), 2.24 - 2.13 (m, 2H), 2.05 - 1.90 (m, 3H), 1.87 - 1.79 (m, 1H), 1.76 - 1.65 (m, 2H), 1.16 - 1.02 (m, 2H), 0.95 - 0.88 (m, 3H); LCMS (ESI ⁺): m/z 560.3 [M+H] ⁺ .
65		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-methylpyridin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.55 (s, 1H), 8.58 - 8.45 (m, 1H), 7.98 - 7.84 (m, 1H), 7.49 (s, 1H), 7.38 - 7.25 (m, 1H), 7.01 - 6.91 (m, 1H), 6.78 - 6.66 (m, 1H), 4.24 - 4.11 (m, 2H), 3.78 - 3.70 (m, 2H), 3.51 - 3.46 (m, 2H), 2.86 - 2.76 (m, 3H), 2.75 - 2.65 (m, 2H), 2.62 - 2.54 (m, 2H), 2.48 - 2.45 (m, 1H), 2.40 - 2.31 (m, 1H), 2.27 - 2.16 (m, 2H), 2.15 - 2.08 (m, 3H), 1.99 - 1.89 (m, 2H), 1.84 - 1.75 (m, 1H), 1.73 - 1.58 (m, 2H), 1.14 - 0.97 (m, 2H), 0.96 - 0.90 (m, 3H); LCMS (ESI ⁺): m/z 549.4 [M+H] ⁺ .
66		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.54 (s, 1H), 8.51 (d, <i>J</i> = 7.2 Hz, 1H), 7.59 (d, <i>J</i> = 9.0 Hz, 1H), 7.48 (s, 1H), 7.39 (d, <i>J</i> = 11.9 Hz, 1H), 6.96 (d, <i>J</i> = 5.5 Hz, 1H), 3.92 (s, 2H), 3.74 (t, <i>J</i> = 6.6 Hz, 3H), 3.59 - 3.42 (m, 2H), 3.03 - 2.71 (m, 4H), 2.63 (d, <i>J</i> = 35.0 Hz, 4H), 2.41 - 2.15 (m, 4H), 2.07 - 1.60 (m, 3H), 1.24 (s, 2H), 0.94 (d, <i>J</i> = 6.1 Hz, 3H). LCMS (ESI ⁺): m/z 603.7 [M+H] ⁺ .

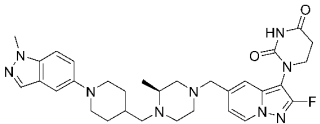
67		1-(2-fluoro-5-(((S)-3-methyl-4-(((S)-1-(5-methylpyrimidin-2-yl)pyrrolidin-3-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.59 (d, $J = 7.2$ Hz, 1H), 8.22 (s, 2H), 7.56 (s, 1H), 7.31 – 6.83 (m, 1H), 4.01 – 3.74 (m, 5H), 3.47 – 3.30 (m, 2H), 3.28 – 2.95 (m, 4H), 2.80 (t, $J = 6.7$ Hz, 2H), 2.70 (d, $J = 14.5$ Hz, 2H), 2.34 (s, 2H), 2.09 (s, 5H), 1.75 (t, $J = 10.3$ Hz, 2H), 1.26 (d, $J = 11.1$ Hz, 4H). LCMS (ESI$^+$): m/z 536.24 [M+H]$^+$.
69		1-(2-fluoro-5-(((3S)-3-methyl-4-((8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.51 (d, $J = 7.1$ Hz, 1H), 8.32 (d, $J = 4.7$ Hz, 2H), 7.49 (s, 1H), 6.95 (dd, $J = 7.3, 1.8$ Hz, 1H), 6.57 (t, $J = 4.8$ Hz, 1H), 4.63 (s, 2H), 3.75 (t, $J = 6.7$ Hz, 3H), 3.46 (s, 2H), 2.79 (t, $J = 6.6$ Hz, 3H), 2.68 (s, 2H), 2.37 – 2.06 (m, 5H), 1.98 – 1.48 (m, 6H), 1.37 – 1.12 (m, 2H), 0.88 (d, $J = 6.1$ Hz, 3H). LCMS (ESI$^+$): m/z 562.5 [M+H]$^+$.
70		(S)-1-(2-fluoro-5-(((4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, Chloroform-d) δ 8.11 (d, $J = 5.1$ Hz, 3H), 7.46 (s, 1H), 7.14 (s, 1H), 6.84 (s, 1H), 4.57 (d, $J = 13.3$ Hz, 2H), 3.78 (t, $J = 6.7$ Hz, 3H), 3.41 (s, 2H), 2.96 – 2.71 (m, 3H), 2.55 (s, 3H), 2.32 – 2.10 (m, 2H), 2.04 – 1.78 (m, 3H), 1.67 (s, 2H), 1.21 (d, $J = 21.6$ Hz, 3H), 1.07 (s, 2H), 0.87 (d, $J = 43.5$ Hz, 2H). LCMS (ESI$^+$): m/z 554.5 [M+H]$^+$.
71		(S)-1-(2-fluoro-5-(((3-methyl-4-((1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyri

		midine-2,4(1H,3H)-dione; ^1H NMR (600 MHz, DMSO- d_6) δ 10.57 (s, 1H), 8.66 (s, 2H), 8.52 (d, J = 7.1 Hz, 1H), 8.22 (s, 0H), 7.49 (s, 1H), 6.96 (d, J = 7.0 Hz, 1H), 4.70 (dq, J = 12.2, 3.8 Hz, 2H), 3.74 (t, J = 6.7 Hz, 2H), 3.09 – 2.88 (m, 2H), 2.88 – 2.72 (m, 3H), 2.59 (dd, J = 26.9, 10.7 Hz, 3H), 2.43 – 2.12 (m, 4H), 2.06 – 1.61 (m, 6H), 1.33 – 0.76 (m, 6H). LCMS (ESI $^+$): m/z 604.34 [M+H] $^+$.
72		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(4-methylpyrimidin-2-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO- d_6) δ 10.57 (s, 1H), 8.53 (d, J = 7.1 Hz, 1H), 8.26 – 8.02 (m, 1H), 7.50 (d, J = 1.8 Hz, 1H), 6.98 (dd, J = 7.3, 1.8 Hz, 1H), 6.46 (d, J = 4.9 Hz, 1H), 4.66 (d, J = 12.5 Hz, 2H), 3.76 (t, J = 6.7 Hz, 2H), 3.49 (d, J = 4.0 Hz, 2H), 2.95 – 2.79 (m, 2H), 2.59 (d, J = 12.9 Hz, 1H), 2.35 (s, 2H), 2.10 – 1.57 (m, 3H), 1.44 – 1.18 (m, 2H), 1.19 – 0.71 (m, 2H). LCMS (ESI $^+$): m/z 550.5 [M+H] $^+$.
73		(S)-1-(5-((4-((1-(5-cyclopropylpyrimidin-2-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO- d_6) δ 10.57 (s, 1H), 8.53 (d, J = 7.1 Hz, 1H), 8.15 (d, J = 3.0 Hz, 2H), 7.51 (s, 1H), 6.98 (dd, J = 7.2, 1.8 Hz, 1H), 4.59 (d, J = 13.3 Hz, 2H), 3.76 (t, J = 6.7 Hz, 2H), 3.51 (s, 2H), 2.81 (q, J = 7.0 Hz, 3H), 2.63 (s, 2H), 2.30 (s, 2H), 2.06 (d, J = 25.8 Hz, 2H), 1.91 – 1.61 (m, 5H), 1.26 (d, J = 5.6 Hz, 2H), 1.10 – 0.79 (m, 3H), 0.75 – 0.55 (m, 2H). LCMS (ESI $^+$): m/z 576.5 [M+H] $^+$.
74		1-(2-fluoro-5-(((S)-3-methyl-4-(((1R,*5S,*6r)-3-(pyrimidin-2-yl)-3-azabicyclo[3.1.1]heptan-6-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO- d_6) δ 10.57 (s, 1H), 8.53 (d, J = 7.1 Hz, 1H), 8.15 (d, J = 3.0 Hz, 2H), 7.51 (s, 1H), 6.98 (dd, J = 7.2, 1.8 Hz, 1H), 4.59 (d, J = 13.3 Hz, 2H), 3.76 (t, J = 6.7 Hz, 2H), 3.51 (s, 2H), 2.81 (q, J = 7.0 Hz, 3H), 2.63 (s, 2H), 2.30 (s, 2H), 2.06 (d, J = 25.8 Hz, 2H), 1.91 – 1.61 (m, 5H), 1.26 (d, J = 5.6 Hz, 2H), 1.10 – 0.79 (m, 3H), 0.75 – 0.55 (m, 2H). LCMS (ESI $^+$): m/z 576.5 [M+H] $^+$.

		yl) dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.55 (br. s., 1H), 8.50 (d, <i>J</i> = 7.2 Hz, 1H), 8.38 (d, <i>J</i> = 4.8 Hz, 2H), 7.47 (s, 1H), 6.94 (dd, <i>J</i> = 1.6, 7.2 Hz, 1H), 6.65 (t, <i>J</i> = 4.8 Hz, 1H), 3.77 - 3.48 (m, 7H), 3.47 - 3.44 (m, 2H), 2.86 - 2.76 (m, 3H), 2.73 - 2.66 (m, 1H), 2.65 - 2.59 (m, 1H), 2.57 - 2.53 (m, 1H), 2.50 - 2.46 (m, 2H), 2.44 - 2.38 (m, 1H), 2.22 - 2.12 (m, 2H), 2.06 - 1.95 (m, 2H), 1.92 - 1.83 (m, 1H), 1.35 (d, <i>J</i> = 9.2 Hz, 1H), 0.87 - 0.79 (m, 3H). LCMS (ESI ⁺): <i>m/z</i> 548.4 [M+H] ⁺ .
75		1-(2-fluoro-5-(((<i>S</i>)-3-methyl-4-(((1 <i>R</i> ,*5 <i>S</i> ,*6 <i>s</i>)-3-(pyrimidin-2-yl)-3-azabicyclo[3.1.1]heptan-6-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5- <i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.49 (br. s., 1H), 8.49 (d, <i>J</i> = 7.2 Hz, 1H), 8.36 (d, <i>J</i> = 4.8 Hz, 2H), 7.47 (s, 1H), 6.96 (dd, <i>J</i> = 1.6, 7.2 Hz, 1H), 6.63 (t, <i>J</i> = 4.8 Hz, 1H), 3.79 - 3.60 (m, 7H), 3.49 - 3.45 (m, 2H), 3.06 - 2.98 (m, 1H), 2.78 (t, <i>J</i> = 6.8 Hz, 3H), 2.62 - 2.56 (m, 2H), 2.40 - 2.31 (m, 3H), 2.30 - 2.18 (m, 3H), 2.02 - 1.93 (m, 1H), 1.91 - 1.82 (m, 1H), 1.37 - 1.30 (m, 1H), 1.04 - 0.97 (m, 3H). LCMS (ESI ⁺): <i>m/z</i> 548.4 [M+H] ⁺ .
76		(<i>S</i>)-1-(2-fluoro-5-((3-methyl-4-((1-(2-methyl-2 <i>H</i> -indazol-5-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5- <i>a</i>]pyridin-3-yl)dihydropyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.53 (s, 1H), 8.50 (dd, <i>J</i> = 7.0, 0.8 Hz, 1H), 8.04 (d, <i>J</i> = 0.8 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.42 (d, <i>J</i> = 9.3 Hz, 1H), 7.07 (dd, <i>J</i> = 9.4, 2.2 Hz, 1H), 6.96 (dd, <i>J</i> = 7.2, 1.8 Hz, 1H), 6.86 (d, <i>J</i> = 2.1 Hz, 1H),

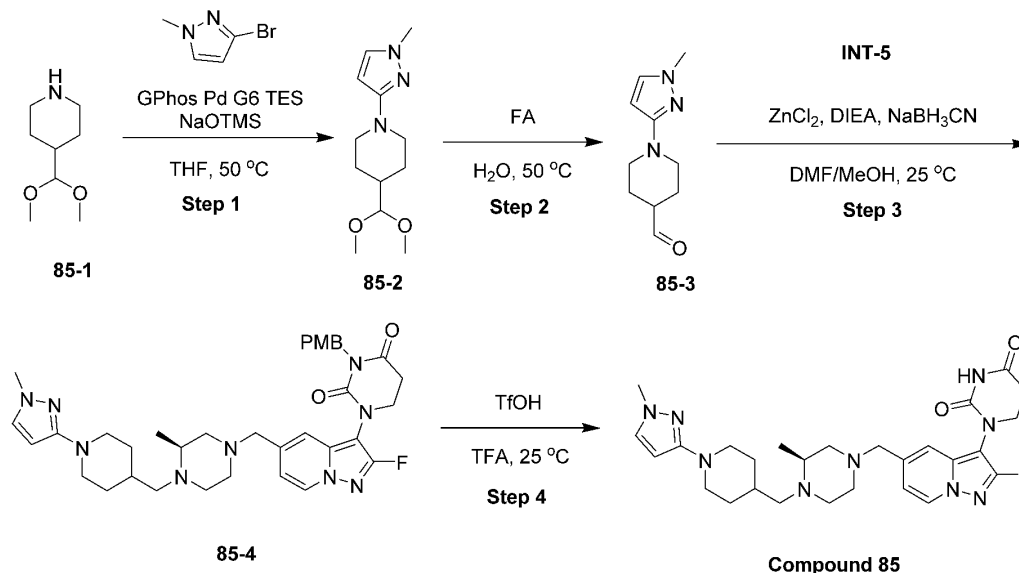
		4.08 (s, 3H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.50 (dd, $J = 18.3, 8.7$ Hz, 5H), 2.80 (q, $J = 7.8, 6.7$ Hz, 3H), 2.56 (ddd, $J = 15.0, 9.1, 2.8$ Hz, 4H), 2.40 (s, 1H), 2.22 (q, $J = 9.8, 8.0$ Hz, 2H), 2.05 – 1.92 (m, 2H), 1.87 (d, $J = 12.9$ Hz, 1H), 1.72 (d, $J = 12.6$ Hz, 1H), 1.57 (s, 1H), 1.34 – 1.14 (m, 2H), 0.97 (d, $J = 6.1$ Hz, 3H). LCMS (ESI ⁺): m/z 588.5 [M+H] ⁺ .
77		(S)-3-chloro-4-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)benzonitrile; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.54 (s, 1H), 8.54 (d, $J = 7.1$ Hz, 1H), 7.92 (d, $J = 2.0$ Hz, 1H), 7.73 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.51 (s, 1H), 7.23 (d, $J = 8.5$ Hz, 1H), 6.97 (dd, $J = 7.2, 1.9$ Hz, 1H), 3.75 (t, $J = 6.7$ Hz, 2H), 3.63 – 3.52 (m, 2H), 3.44 (d, $J = 11.7$ Hz, 3H), 2.84 – 2.65 (m, 6H), 1.95 (dd, $J = 36.2, 10.4$ Hz, 2H), 1.76 (d, $J = 12.7$ Hz, 2H), 1.44 – 1.04 (m, 10H). LCMS (ESI ⁺): m/z 593.5 [M+H] ⁺ .
78		(S)-2-chloro-4-(4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidin-1-yl)benzonitrile; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.54 (s, 1H), 8.53 (d, $J = 7.1$ Hz, 1H), 8.0 (d, $J = 2.0$ Hz, 1H), 7.61 (d, $J = 9.0$ Hz, 1H), 7.50 (s, 1H), 7.11 (d, $J = 2.5$ Hz, 1H), 6.96 (dt, $J = 8.9, 2.3$ Hz, 2H), 3.97 (d, $J = 13.0$ Hz, 2H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.54 (s, 2H), 2.90 (q, $J = 12.2, 11.5$ Hz, 3H), 2.79 (t, $J = 6.7$ Hz, 3H), 2.68 (s, 3H), 2.38 (s, 2H), 1.83 (d, $J = 13.4$ Hz, 2H), 1.68 (d, $J = 13.0$ Hz, 1H), 1.28 – 1.22 (m, 2H), 1.20 – 1.11 (m, 2H), 1.07 (s, 3H). LCMS (ESI ⁺): m/z 593.5 [M+H] ⁺ .

79		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(2,4,5-trifluorophenyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.54 (s, 1H), 8.55 (s, 1H), 7.51 (s, 2H), 7.12 (s, 1H), 6.96 (d, $J = 7.2$ Hz, 1H), 3.75 (t, $J = 6.7$ Hz, 2H), 3.55 (d, $J = 58.3$ Hz, 3H), 2.94 (s, 2H), 2.79 (t, $J = 6.7$ Hz, 3H), 2.61 (s, 4H), 2.25 (d, $J = 37.2$ Hz, 2H), 1.89 (d, $J = 14.0$ Hz, 3H), 1.70 (s, 1H), 1.55 (s, 1H), 1.45 – 1.10 (m, 6H). LCMS (ESI^+): m/z 588.5 $[\text{M}+\text{H}]^+$.
80		(S)-1-(2-fluoro-5-((4-((1-(2-fluoro-4-methylphenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.54 (s, 1H), 8.56 (d, $J = 7.2$ Hz, 1H), 7.51 (s, 1H), 7.01 – 6.83 (m, 4H), 3.75 (t, $J = 6.7$ Hz, 2H), 3.55 (d, $J = 59.8$ Hz, 3H), 3.19 – 2.88 (m, 3H), 2.79 (t, $J = 6.7$ Hz, 3H), 2.60 (s, 4H), 2.30 (s, 1H), 2.22 (s, 3H), 2.01 – 1.80 (m, 3H), 1.70 (s, 1H), 1.58 – 1.13 (m, 7H). LCMS (ESI^+): m/z 566.5 $[\text{M}+\text{H}]^+$.
81		(S)-1-(2-fluoro-5-((4-((1-(2-fluoro-4-(trifluoromethyl)phenyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.54 (s, 1H), 8.55 (s, 1H), 7.50 (s, 2H), 7.45 (d, $J = 8.2$ Hz, 1H), 7.17 (s, 1H), 7.01 – 6.90 (m, 1H), 3.75 (t, $J = 6.7$ Hz, 2H), 3.69 – 3.42 (m, 5H), 2.94 (s, 2H), 2.79 (t, $J = 6.7$ Hz, 5H), 2.57 (s, 2H), 2.21 (s, 1H), 2.04 – 1.81 (m, 3H), 1.79 – 1.56 (m, 2H), 1.39 – 1.14 (m, 5H). LCMS (ESI^+): m/z 620.5 $[\text{M}+\text{H}]^+$.

82		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(1-methyl-1H-indazol-5-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.53 (s, 1H), 8.50 (d, $J = 7.2$ Hz, 1H), 8.20 (s, 1H, FA), 7.83 (d, $J = 0.9$ Hz, 1H), 7.50 – 7.41 (m, 2H), 7.20 (dd, $J = 9.2, 2.2$ Hz, 1H), 7.06 (d, $J = 2.1$ Hz, 1H), 6.96 (dd, $J = 7.1, 1.8$ Hz, 1H), 3.97 (s, 3H), 3.74 (t, $J = 6.7$ Hz, 3H), 3.47 (d, $J = 5.1$ Hz, 3H), 2.79 (q, $J = 6.5$ Hz, 3H), 2.59 (ddt, $J = 17.7, 8.8, 4.3$ Hz, 4H), 2.38 (s, 1H), 2.20 (q, $J = 9.0$ Hz, 2H), 2.06 – 1.92 (m, 2H), 1.88 (d, $J = 12.7$ Hz, 1H), 1.72 (d, $J = 13.0$ Hz, 1H), 1.57 (d, $J = 4.2$ Hz, 1H), 1.35 – 1.14 (m, 2H), 0.96 (d, $J = 6.1$ Hz, 3H). LCMS (ESI^+): m/z 588.7 $[\text{M}+\text{H}]^+$.
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Example 21: Preparation of compound 85:

**3-(2-fluoro-5-(((S)-3-methyl-4-((1-(1-methyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)pi
perazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-2,6-dione**



5 Step 1: Synthesis of 4-(dimethoxymethyl)-1-(1-methyl-1H-pyrazol-3-yl)piperidine

A mixture of 4-(dimethoxymethyl)piperidine (119 mg, 0.75 mmol), 3-bromo-1-methyl-1H-pyrazole (119 mg, 0.75 mmol), NaOTMS (85 mg, 0.79 mmol) and GPhos Pd G6 TES (CAS: 2489525-81-5, 37.6 mg, 0.04 mmol) in THF (20 mL) under nitrogen atmosphere was heated at 50 °C for 3 hrs. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum ether/Ethyl acetate @36 ml/min). Compound 4-(dimethoxymethyl)-1-(1-methyl-1H-pyrazol-3-yl)piperidine (50 mg, 28% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 240.3 [M+H]⁺.

15 Step 2: Synthesis of 1-(1-methyl-1H-pyrazol-3-yl)piperidine-4-carbaldehyde

A mixture of 4-(dimethoxymethyl)-1-(1-methyl-1H-pyrazol-3-yl)piperidine (50 mg, 0.21 mmol), FA (3 mL) in H₂O (1 mL) was stirred at 50 °C for 1 hr. The reaction was quenched with aq. NaHCO₃ (20 mL) and extracted with EA (15 mLx2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum ether/Ethyl acetate @36 ml/min). Compound 1-(1-methyl-1H-pyrazol-3-yl)piperidine-4-carbaldehyde (25 mg, 63% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 194.3 [M+H]⁺.

Step 3: Synthesis of**3-(2-fluoro-5-(((S)-3-methyl-4-((1-(1-methyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione**

A mixture of

(S)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (31 mg, 0.06 mmol),

1-(1-methyl-1H-pyrazol-3-yl)piperidine-4-carbaldehyde (25 mg, 0.13 mmol) and DIEA (17 mg, 0.13 mmol) in MeOH (5 mL) was stirred for 10 min at the room temperature.

ZnCl₂ (0.2 mL, 0.4 mmol, 2 M in THF) was added, the mixture was stirred overnight at the room temperature. Then sodium cyanoborohydride (8 mg, 0.13 mmol) was added, the reaction mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel

chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound

3-(2-fluoro-5-(((S)-3-methyl-4-((1-(1-methyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione (35 mg, 83% yield) was obtained as a yellow oil. LCMS (ESI⁺): m/z 658.6 [M+H]⁺.

Step 4: Synthesis of**3-(2-fluoro-5-(((S)-3-methyl-4-((1-(1-methyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-2,6-dione**

A mixture of

3-(2-fluoro-5-(((S)-3-methyl-4-((1-(1-methyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-1-(4-methoxybenzyl)piperidine-2,6-dione

(35 mg, 0.05 mmol), TfOH (2 mL) in TFA (2 mL) was stirred at 30 °C for 1 hr. The reaction was quenched with aq. NaHCO₃ (30 mL), extracted with EA (15 mLx2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica

gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound

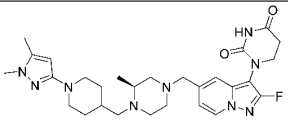
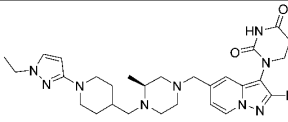
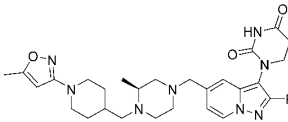
3-(2-fluoro-5-(((S)-3-methyl-4-((1-(1-methyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-2,6-dione (12 mg, 41% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.55 (s, 1H), 8.52 (d, *J* = 7.1 Hz, 1H), 7.49 (t, *J* = 2.2 Hz, 2H), 6.96 (dd, *J* = 7.1, 1.8 Hz, 1H), 5.99 (d, *J* = 2.1 Hz, 1H),

3.74 (d, $J = 4.7$ Hz, 8H), 3.04 (s, 2H), 2.79 (t, $J = 6.7$ Hz, 3H), 2.73 – 2.62 (m, 3H), 2.39 (d, $J = 34.3$ Hz, 2H), 2.12 (s, 1H), 1.91 (d, $J = 12.9$ Hz, 4H), 1.73 (d, $J = 12.9$ Hz, 1H), 1.55 (s, 1H), 1.42 – 1.20 (m, 3H), 1.06 (d, $J = 6.6$ Hz, 2H). LCMS (ESI⁺): m/z 538.5 [M+H]⁺.

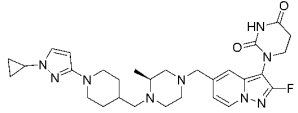
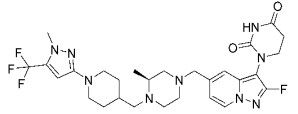
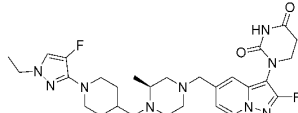
- 5 **Example 22:** The following compounds in **Table 8** were prepared according to the procedures described for the **compound 85** using the appropriate heteroaryl fragments.

Table 8

No.	Structure	Compound name and characterization
86		(S)-1-(5-((4-((1-(1,2,4-thiadiazol-5-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 10.49 (s, 1H), 8.44 (d, $J = 7.1$ Hz, 1H), 7.91 (s, 1H), 7.42 (s, 1H), 6.89 (d, $J = 7.1$ Hz, 1H), 3.67 (t, $J = 6.7$ Hz, 2H), 3.40 (q, $J = 14.1$ Hz, 3H), 3.12 (q, $J = 13.6$ Hz, 2H), 2.72 (d, $J = 6.7$ Hz, 2H), 2.50 (s, 2H), 2.30 (d, $J = 20.1$ Hz, 1H), 2.12 (s, 3H), 2.03 – 1.61 (m, 5H), 1.39 – 0.98 (m, 4H), 0.87 (d, $J = 6.1$ Hz, 3H). LCMS (ESI ⁺): m/z 542.5 [M+H] ⁺ .
87		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(thiazol-4-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.54 (s, 1H), 8.84 (d, $J = 2.1$ Hz, 1H), 8.51 (d, $J = 7.1$ Hz, 1H), 7.49 (s, 1H), 6.96 (dd, $J = 7.1, 1.8$ Hz, 1H), 6.21 (s, 1H), 3.82 (d, $J = 11.9$ Hz, 2H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.49 (d, $J = 13.9$ Hz, 2H), 2.78 (t, $J = 6.7$ Hz, 3H), 2.71 – 2.54 (m, 3H), 2.36 (s, 1H), 2.20 (s, 2H), 2.02 – 1.94 (m, 2H), 1.83 (d, $J = 13.0$ Hz, 1H), 1.72 – 1.53 (m, 2H), 1.45 (t, $J = 7.8$ Hz, 1H), 1.24 (d, $J = 3.5$ Hz, 3H), 0.94 (s, 3H). LCMS (ESI ⁺): m/z 541.5 [M+H] ⁺ .
88		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(1-methyl-1H-1,2,4-triazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 10.49 (s, 1H), 8.44 (d, $J = 7.1$ Hz, 1H), 7.91 (s, 1H), 7.42 (s, 1H), 6.89 (d, $J = 7.1$ Hz, 1H), 3.67 (t, $J = 6.7$ Hz, 2H), 3.40 (q, $J = 14.1$ Hz, 3H), 3.12 (q, $J = 13.6$ Hz, 2H), 2.72 (d, $J = 6.7$ Hz, 2H), 2.50 (s, 2H), 2.30 (d, $J = 20.1$ Hz, 1H), 2.12 (s, 3H), 2.03 – 1.61 (m, 5H), 1.39 – 0.98 (m, 4H), 0.87 (d, $J = 6.1$ Hz, 3H). LCMS (ESI ⁺): m/z 542.5 [M+H] ⁺ .

		(1H,3H)-dione; ^1H NMR (400 MHz, DMSO- d_6) δ 10.57 (s, 1H), 8.58 (d, $J = 7.1$ Hz, 1H), 8.08 (s, 1H), 7.54 (s, 1H), 6.98 (dd, $J = 7.1, 1.9$ Hz, 1H), 3.91 (dd, $J = 12.4, 3.5$ Hz, 3H), 3.77 – 3.74 (m, 12H), 3.66 (s, 3H), 3.03 (d, $J = 42.6$ Hz, 2H), 2.84 – 2.65 (m, 4H), 1.80 (s, 2H), 1.62 (d, $J = 12.4$ Hz, 1H), 1.29 – 1.16 (m, 2H). LCMS (ESI $^+$): m/z 539.4 [M+H] $^+$.
89		(S)-1-(5-((4-((1-(1,5-dimethyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO- d_6) δ 10.58 (s, 1H), 8.58 (d, $J = 7.1$ Hz, 1H), 7.55 (s, 1H), 7.02 – 6.93 (m, 1H), 5.56 (s, 1H), 3.75 (t, $J = 6.7$ Hz, 2H), 3.69 (d, $J = 13.3$ Hz, 1H), 3.60 (d, $J = 12.4$ Hz, 3H), 3.53 (s, 3H), 2.93 (d, $J = 36.0$ Hz, 4H), 2.79 (t, $J = 6.7$ Hz, 2H), 2.70 – 2.53 (m, 4H), 2.43 – 2.29 (m, 1H), 2.15 (s, 3H), 1.82 (d, $J = 14.3$ Hz, 3H), 1.62 (d, $J = 12.6$ Hz, 1H), 1.25 (d, $J = 10.9$ Hz, 6H). LCMS (ESI $^+$): m/z 552.5 [M+H] $^+$.
90		(S)-1-(5-((4-((1-(1-ethyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO- d_6) δ 10.55 (s, 1H), 8.53 (d, $J = 7.1$ Hz, 1H), 7.50 (s, 1H), 7.43 (d, $J = 2.3$ Hz, 1H), 6.96 (dd, $J = 7.2, 1.8$ Hz, 1H), 5.63 (d, $J = 2.3$ Hz, 1H), 3.90 (q, $J = 7.2$ Hz, 2H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.66 – 3.50 (m, 6H), 2.79 (t, $J = 6.7$ Hz, 3H), 2.70 (d, $J = 10.7$ Hz, 2H), 2.60 – 2.52 (m, 2H), 2.40 (s, 2H), 2.17 (s, 1H), 1.80 (d, $J = 12.9$ Hz, 1H), 1.64 (d, $J = 13.4$ Hz, 2H), 1.28 (t, $J = 7.2$ Hz, 4H), 1.25 – 1.13 (m, 2H), 1.10 (d, $J = 6.2$ Hz, 3H). LCMS (ESI $^+$): m/z 552.5 [M+H] $^+$.
91		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(5-methylisoxazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO- d_6) δ 10.57 (s, 1H), 8.58 (d, $J = 7.1$ Hz, 1H), 8.08 (s, 1H), 7.54 (s, 1H), 6.98 (dd, $J = 7.1, 1.9$ Hz, 1H), 3.91 (dd, $J = 12.4, 3.5$ Hz, 3H), 3.77 – 3.74 (m, 12H), 3.66 (s, 3H), 3.03 (d, $J = 42.6$ Hz, 2H), 2.84 – 2.65 (m, 4H), 1.80 (s, 2H), 1.62 (d, $J = 12.4$ Hz, 1H), 1.29 – 1.16 (m, 2H). LCMS (ESI $^+$): m/z 539.4 [M+H] $^+$.

		zolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; LCMS (ESI ⁺): m/z 539.5 [M+H] ⁺ .
92		(S)-1-(2-fluoro-5-((4-((1-(1-isopropyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.54 (s, 1H), 8.51 (d, <i>J</i> = 7.1 Hz, 1H), 7.49 (s, 1H), 7.44 (d, <i>J</i> = 2.3 Hz, 1H), 6.96 (dd, <i>J</i> = 7.2, 1.8 Hz, 1H), 5.61 (d, <i>J</i> = 2.4 Hz, 1H), 4.23 (p, <i>J</i> = 6.6 Hz, 1H), 3.74 (t, <i>J</i> = 6.7 Hz, 2H), 3.63 – 3.55 (m, 3H), 3.48 (d, <i>J</i> = 4.4 Hz, 2H), 2.78 (t, <i>J</i> = 6.7 Hz, 3H), 2.67 – 2.52 (m, 5H), 2.25 (s, 2H), 2.01 (s, 1H), 1.79 (d, <i>J</i> = 13.1 Hz, 1H), 1.68 – 1.45 (m, 3H), 1.32 (d, <i>J</i> = 6.6 Hz, 6H), 1.21 – 1.04 (m, 2H), 0.97 (d, <i>J</i> = 6.1 Hz, 3H). LCMS (ESI ⁺): m/z 566.5 [M+H] ⁺ .
93		(S)-1-(2-fluoro-5-((3-methyl-4-((1-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.55 (s, 1H), 8.52 (d, <i>J</i> = 7.1 Hz, 1H), 7.56 (d, <i>J</i> = 2.4 Hz, 1H), 7.49 (s, 1H), 6.96 (dd, <i>J</i> = 7.1, 1.8 Hz, 1H), 5.82 (d, <i>J</i> = 2.5 Hz, 1H), 4.85 (q, <i>J</i> = 9.1 Hz, 2H), 3.74 (t, <i>J</i> = 6.7 Hz, 2H), 3.65 – 3.59 (m, 2H), 3.51 (s, 2H), 2.95 (s, 1H), 2.78 (t, <i>J</i> = 6.7 Hz, 2H), 2.69 – 2.54 (m, 6H), 2.32 (s, 1H), 1.79 (d, <i>J</i> = 13.1 Hz, 1H), 1.63 (d, <i>J</i> = 12.1 Hz, 2H), 1.25 (t, <i>J</i> = 5.3 Hz, 2H), 1.15 (dd, <i>J</i> = 28.2, 13.2 Hz, 3H), 1.02 (d, <i>J</i> = 6.0 Hz, 3H). LCMS (ESI ⁺): m/z 606.5 [M+H] ⁺ .
94		(S)-1-(2-fluoro-5-((4-((1-(1-isopropyl-5-methyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.57 (s, 1H), 8.53 (d, <i>J</i> = 7.1 Hz, 1H), 7.51 (s, 1H), 6.98 (dd, <i>J</i> = 7.1, 1.8 Hz, 1H), 5.43 (s, 1H), 4.35 – 4.24 (m, 1H),

		3.76 (t, $J = 6.7$ Hz, 2H), 3.66 – 3.15(m, 6H, overlap with water peak), 2.98 – 2.76 (m, 3H), 2.73 – 2.43 (m, 4H, overlap with DMSO peak), 2.37 – 2.22 (m, 2H), 2.15 (s, 3H), 2.10 – 1.95 (m, 1H), 1.80 (d, $J = 12.9$ Hz, 1H), 1.68 – 1.51 (m, 2H), 1.28 (d, $J = 6.5$ Hz, 6H), 1.23 – 0.97 (m, 6H). LCMS (ESI ⁺): m/z 580.6 [M+H] ⁺ .
95		(S)-1-(5-(((4-((1-(1-cyclopropyl-1H-pyrazol-3-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (s, 1H), 8.52 (d, $J = 7.1$ Hz, 1H), 7.50 (s, 1H), 7.46 (d, $J = 2.4$ Hz, 1H), 6.98 (dd, $J = 7.8$ Hz, 1.8 Hz, 1H), 5.64 (d, $J = 2.4$ Hz, 1H), 3.76 (t, $J = 6.7$ Hz, 2H), 3.69 – 3.02 (m, 6H, overlap with water peak), 2.86 – 2.75 (m, 3H), 2.68 – 2.37 (m, 4H, overlap with DMSO peak), 2.29 – 2.16 (m, 2H), 2.05 – 1.90 (m, 2H), 1.85 – 1.73 (m, 1H), 1.69 – 1.48 (m, 2H), 1.26 – 0.80 (m, 10H). LCMS (ESI ⁺): m/z 564.6 [M+H] ⁺ .
96		(S)-1-(2-fluoro-5-(((3-methyl-4-((1-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (s, 1H), 8.54 (d, $J = 7.1$ Hz, 1H), 7.51 (s, 1H), 6.96 (dd, $J = 7.3$, 1.8 Hz, 1H), 6.29 (s, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.69 (s, 3H), 3.57 (d, $J = 20.1$ Hz, 2H), 3.19 – 3.04 (m, 5H), 2.79 (t, $J = 6.7$ Hz, 3H), 2.62 (q, $J = 11.5$ Hz, 3H), 1.88 (d, $J = 12.8$ Hz, 1H), 1.74 (dd, $J = 19.4$, 9.7 Hz, 2H), 1.40 – 1.22 (m, 4H), 1.18 (t, $J = 7.3$ Hz, 4H), 1.10 (s, 1H). LCMS (ESI ⁺): m/z 606.5 [M+H] ⁺ .
97		(S)-1-(5-(((4-((1-(1-ethyl-4-fluoro-1H-pyrazol-3-yl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ

		10.55 (s, 1H), 8.52 (d, $J = 7.1$ Hz, 1H), 7.67 (d, $J = 4.3$ Hz, 1H), 7.50 (s, 1H), 6.96 (d, $J = 7.1$ Hz, 1H), 3.83 (q, $J = 7.2$ Hz, 5H), 3.74 (t, $J = 6.7$ Hz, 6H), 2.77 (dt, $J = 15.0, 8.4$ Hz, 6H), 2.63 (q, $J = 11.1$ Hz, 2H), 2.24 (s, 1H), 1.85 – 1.60 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 8H), 1.14 (d, $J = 6.3$ Hz, 4H). LCMS (ESI ⁺): m/z 570.5 [M+H] ⁺ .
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Example 23: Preparation of compound 98:

(S)-1-(2-fluoro-5-((3-methyl-4-((4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione;

5 **Compound 99:**

1-(2-fluoro-5-(((S)-3-methyl-4-(((1*s,4*R)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; and Compound 100:

10 **1-(2-fluoro-5-(((S)-3-methyl-4-(((1*r,4*S)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**



Step 2: Synthesis of 4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohex-1-en-1-yl (1,1,1,2,3,3,4,4-octafluoro-4I3-butan-2-yl)-12-fluoranesulfonate

A solution of 4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexan-1-one (2.0 g, 8.3 mmol) in 20 mL THF was cooled to 0 °C, DBU (3.8 g, 24.9 mmol) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (3.8 g, 12.5 mmol) were added. The reaction mixture was stirred at 0 °C for 3 hrs. The reaction was quenched with H₂O (100 mL), extracted with EA (50 mLx2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~5% Petroleum ether/Ethyl acetate @45 ml/min). Compound 4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohex-1-en-1-yl (1,1,1,2,3,3,4,4-octafluoro-4I3-butan-2-yl)-12-fluoranesulfonate (2.1 g, 49% yield) was obtained as a colorless oil.

Step 3: Synthesis of

3-(4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohex-1-en-1-yl)-1-methyl-1H-pyrazole

A mixture of 4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohex-1-en-1-yl (1,1,1,2,3,3,4,4-octafluoro-4I3-butan-2-yl)-12-fluoranesulfonate (2.1 g, 4.0 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (832 mg, 4.0 mmol), K₂CO₃ (1.7 g, 12.0 mmol) and Pd(dppf)Cl₂·DCM (327 mg, 0.4 mmol) in 1,4-dioxane/H₂O (10 mL, 4:1) under nitrogen atmosphere was heated at 100 °C for 2 hrs. The reaction was quenched with H₂O (30 mL), extracted with EA (30 mLx2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure give a residue, which was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~15% Petroleum ether/Ethyl acetate @36 ml/min). Compound 3-(4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohex-1-en-1-yl)-1-methyl-1H-pyrazole (550 mg, 49% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 307.4 [M+H]⁺.

Step 4: Synthesis of

3-(4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)-1-methyl-1H-pyrazole

A mixture of 3-(4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohex-1-en-1-yl)-1-methyl-1H-pyrazole (500 mg, 1.6 mmol) and Pd/C (100 mg) in EtOH (10 mL) under hydrogen atmosphere was stirred at room temperature for 2 hrs. The mixture was filtered through celite pad. The filtrate was concentrated under reduced pressure to give a colorless oil (500 mg, 99% yield), which was used in the next step without further purification. LCMS (ESI⁺): m/z 309.5 [M+H]⁺.

Step 5: Synthesis of (4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methanol

To a solution of

3-(4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)-1-methyl-1H-pyrazole (500 mg, 1.6 mmol) in 10 mL THF was added TBAF (1N, 8 mL, 8.0 mmol). The mixture was stirred at room temperature for 1 hr. The reaction was poured into H₂O (50 mL), extracted with EA (20 mLx2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless oil (300 mg, 98% yield), which was used in the next step without further purification. LCMS (ESI⁺): m/z 195.4 [M+H]⁺.

Step 6: Synthesis of 4-(1-methyl-1H-pyrazol-3-yl)cyclohexane-1-carbaldehyde

A solution of 4-(1-methyl-1H-pyrazol-3-yl)cyclohexylmethanol (310 mg, 1.6 mmol) in 10 mL DCM was cooled to 0 °C. DMP (1016 mg, 2.4 mmol) was added. The reaction mixture was stirred at room temperature for 1 hr. The mixture was poured into aq. NaHCO₃ (30 mL), extracted with DCM (15 mLx2). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum ether/Ethyl acetate @36 ml/min). Compound 4-(1-methyl-1H-pyrazol-3-yl)cyclohexane-1-carbaldehyde (280 mg, 91% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 193.3 [M+H]⁺.

Step 7: Synthesis of

(S)-1-(2-fluoro-5-((3-methyl-4-((4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

A mixture of

(S)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (200 mg, 0.42 mmol), 4-(1-methyl-1H-pyrazol-3-yl)cyclohexane-1-carbaldehyde (161 mg, 0.84 mmol) and DIEA (108 mg, 0.84 mmol) in MeOH (5 mL) was stirred at room temperature for 10 min. ZnCl₂ (0.5 mL, 1 mmol, 2 M THF solution) was added, the mixture was stirred at room temperature overnight. Then sodium cyanoborohydride (53 mg, 0.84 mmol) was added, the reaction mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound (S)-1-(2-fluoro-5-((3-methyl-4-((4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1

H,3H)-dione (200 mg, 73% yield) was obtained as a yellow oil. LCMS (ESI⁺): m/z 657.6 [M+H]⁺.

Step 8: Synthesis of

(S)-1-(2-fluoro-5-((3-methyl-4-((4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

A mixture of

(S)-1-(2-fluoro-5-((3-methyl-4-((4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (200 mg, 0.30 mmol), TfOH (3 mL) in TFA (3 mL) was stirred at 30 °C for 1

h. The reaction was quenched with aq. NaHCO₃ (50 mL), extracted with EA (30 mLx2).

The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound

(S)-1-(2-fluoro-5-((3-methyl-4-((4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (70 mg, 43% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.55 (s, 1H), 8.52 (d, *J* = 7.1 Hz, 1H), 7.49 (t, *J* = 2.2 Hz, 2H), 6.96 (dd, *J* = 7.1, 1.8 Hz, 1H), 5.99 (d, *J* = 2.1 Hz, 1H), 3.74 (d, *J* = 4.7 Hz, 8H), 3.04 (s, 2H), 2.79 (t, *J* = 6.7 Hz, 3H), 2.73 – 2.62 (m, 3H), 2.39 (d, *J* = 34.3 Hz, 2H), 2.12 (s, 1H), 1.91 (d, *J* = 12.9 Hz, 4H), 1.73 (d, *J* = 12.9 Hz, 1H), 1.55 (s, 1H), 1.42 – 1.20 (m, 3H), 1.06 (d, *J* = 6.6 Hz, 3H). LCMS (ESI⁺): m/z 537.5 [M+H]⁺.

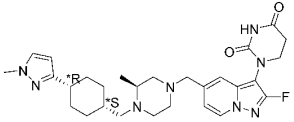
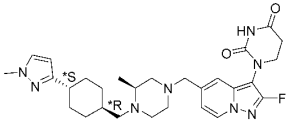
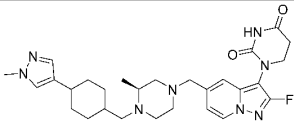
Step 9: Chiral separation of Compound 99 and 100

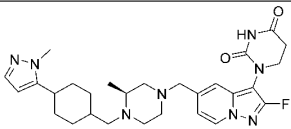
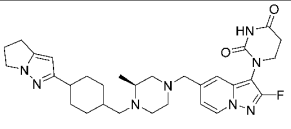
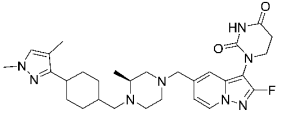
The compound **98** (540 mg, 1.01 mmol) was separated by prep-SFC (DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO₂-EtOH]; B:40%, isocratic elution mode; A/B = 1/1 at 1.0 mL/ min; Temp: 35 °C; Wavelength: 254 nm). Compound **99** (25 mg, 13.82 %) as peak **1** was obtained as a white solid, Rt= 0.54 min. Compound **100** (230 mg, 14.47 %) as peak **2** was obtained as a white solid, Rt= 0.95 min.

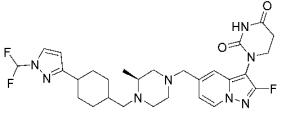
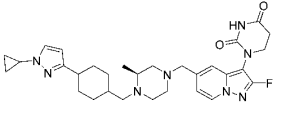
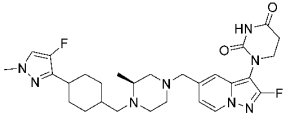
Example 24: The compounds in **Table 9** were prepared according to the procedures of the compound **98**.

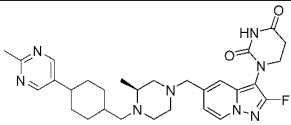
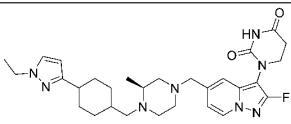
Table 9

No.	Structure	Compound name and characterization
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99		1-(2-fluoro-5-(((S)-3-methyl-4-(((1^s,4^R)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) 10.54 (s, 1 H), 8.46 - 8.56 (m, 1 H), 7.49 (d, <i>J</i>=6.80 Hz, 2 H), 6.92 - 6.97 (m, 1 H), 6.00 - 6.09 (m, 1 H), 3.67 - 3.82 (m, 5 H), 3.53 - 3.65 (m, 1 H), 3.44 - 3.50 (m, 1 H), 3.17 - 3.29 (m, 2 H), 2.87 - 2.97 (m, 1 H), 2.73 - 2.83 (m, 3 H), 2.55 - 2.63 (m, 2 H), 2.06 - 2.27 (m, 2 H), 1.80 - 2.03 (m, 3H), 1.58 - 1.78 (m, 4 H), 1.45 - 1.57 (m, 2 H), 1.27 - 1.44 (m, 3 H), 0.88 - 0.98 (m, 2 H). LCMS (ESI⁺): <i>m/z</i> 537.4 [M+H]⁺. Chiral Column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO₂-EtOH]; B:50%, isocratic elution mode; RT= 0.54 min
100		1-(2-fluoro-5-(((S)-3-methyl-4-(((1^r,4^S)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.55 (s, 1H), 8.57 (d, <i>J</i> = 7.1 Hz, 1H), 7.54 (d, <i>J</i> = 2.1 Hz, 1H), 7.51 (d, <i>J</i> = 2.1 Hz, 1H), 6.98 (dd, <i>J</i> = 7.1, 1.9 Hz, 1H), 6.00 (d, <i>J</i> = 2.2 Hz, 1H), 3.75 (d, <i>J</i> = 5.1 Hz, 5H), 3.67 (s, 4H), 3.17 (s, 3H), 2.97 (s, 3H), 2.80 (t, <i>J</i> = 6.7 Hz, 3H), 2.38 (s, 1H), 2.00 - 1.87 (m, 3H), 1.74 (d, <i>J</i> = 11.5 Hz, 2H), 1.45 - 1.34 (m, 2H), 1.27 (d, <i>J</i> = 6.1 Hz, 3H), 1.19 - 1.02 (m, 2H). LCMS (ESI⁺): <i>m/z</i> 537.5 [M+H]⁺. Chiral analysis: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO₂-EtOH]; B:40%, isocratic elution mode; A/B = 1/1 at 1.0 mL/min; Temp: 35 °C; Wavelength: 254 nm. Purity, 90.82%, RT=0.95 min.
101		(S)-1-(2-fluoro-5-((3-methyl-4-((4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

		ione; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.55 (s, 1H), 8.52 (d, $J = 7.1$ Hz, 1H), 7.49 (s, 1H), 7.42 (s, 1H), 7.23 (s, 1H), 6.96 (dd, $J = 7.2, 1.8$ Hz, 1H), 3.74 (d, $J = 2.6$ Hz, 8H), 3.51 (s, 4H), 2.78 (t, $J = 6.7$ Hz, 3H), 2.64 (s, 2H), 2.34 (td, $J = 13.7, 12.8, 6.7$ Hz, 3H), 1.89 (d, $J = 12.2$ Hz, 3H), 1.76 – 1.42 (m, 1H), 1.35 – 1.16 (m, 2H), 1.10 – 0.87 (m, 5H). LCMS (ESI^+): m/z 537.6 $[\text{M}+\text{H}]^+$.
102		(S)-1-(2-fluoro-5-((3-methyl-4-((4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.55 (s, 1H), 8.55 (d, $J = 7.1$ Hz, 1H), 7.51 (s, 1H), 7.26 (d, $J = 1.9$ Hz, 1H), 6.97 (dd, $J = 7.1, 1.8$ Hz, 1H), 5.99 (d, $J = 1.9$ Hz, 1H), 3.74 (d, $J = 4.3$ Hz, 6H), 3.59 (s, 2H), 2.91 (s, 2H), 2.79 (t, $J = 6.7$ Hz, 3H), 2.63 (ddd, $J = 12.0, 8.5, 3.4$ Hz, 2H), 2.29 (s, 1H), 1.92 (t, $J = 14.2$ Hz, 3H), 1.81 – 1.59 (m, 3H), 1.38 – 1.28 (m, 2H), 1.28 – 1.22 (m, 2H), 1.19 (d, $J = 6.6$ Hz, 3H), 1.15 – 1.02 (m, 2H). LCMS (ESI^+): m/z 537.6 $[\text{M}+\text{H}]^+$.
103		(S)-1-(5-((4-((4-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.52 (s, 1H), 8.51 (d, $J = 7.1$ Hz, 1H), 7.48 (s, 1H), 6.96 (dd, $J = 7.1, 1.8$ Hz, 1H), 5.74 (s, 1H), 3.94 (t, $J = 7.1$ Hz, 2H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.48 (s, 3H), 2.76 (dt, $J = 16.3, 7.0$ Hz, 5H), 2.58 (s, 2H), 2.48 – 2.40 (m, 4H), 1.99 – 1.82 (m, 5H), 1.72 (d, $J = 12.6$ Hz, 2H), 1.38 – 1.21 (m, 5H), 0.95 (s, 4H). LCMS (ESI^+): m/z 563.7 $[\text{M}+\text{H}]^+$.
104		(S)-1-(5-((4-((4-(1,4-dimethyl-1H-pyrazol-3-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.52 (s, 1H),

		8.50 (d, $J = 7.1$ Hz, 1H), 7.48 (s, 1H), 7.25 (s, 1H), 6.95 (dd, $J = 7.1, 1.8$ Hz, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.66 (s, 3H), 3.53 – 3.40 (m, 2H), 2.78 (t, $J = 6.7$ Hz, 2H), 2.69 – 2.29 (m, 9H), 2.27 – 2.11 (m, 1H), 2.02 – 1.85 (m, 5H), 1.81 – 1.66 (m, 3H), 1.53 – 1.29 (m, 3H), 1.05 – 0.80 (m, 4H). LCMS (ESI ⁺): m/z 551.5 [M+H] ⁺ .
105		(S)-1-(5-((4-((1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.52 (s, 1H), 8.50 (d, $J = 7.1$ Hz, 1H), 8.05 (d, $J = 2.7$ Hz, 1H), 7.68 (t, $J = 59.4$ Hz, 1H), 7.48 (s, 1H), 6.96 (dd, $J = 7.1, 1.8$ Hz, 1H), 6.37 (d, $J = 2.7$ Hz, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.42 (s, 5H), 2.78 (t, $J = 6.7$ Hz, 3H), 2.65 – 2.40 (m, 3H), 2.40 – 2.29 (m, 1H), 2.26 – 2.10 (m, 2H), 1.96 – 1.91 (m, 4H), 1.74 (d, $J = 12.9$ Hz, 1H), 1.57 – 1.28 (m, 3H), 1.08 – 0.83 (m, 4H). LCMS (ESI ⁺): m/z 573.6 [M+H] ⁺ .
106		(S)-1-(5-((4-((1-(cyclopropyl)-1H-pyrazol-3-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.52 (s, 1H), 8.50 (d, $J = 7.1$ Hz, 1H), 7.55 (d, $J = 2.2$ Hz, 1H), 7.47 (s, 1H), 6.95 (dd, $J = 7.2, 1.8$ Hz, 1H), 5.98 (d, $J = 2.3$ Hz, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.56 (tt, $J = 7.4, 3.6$ Hz, 2H), 3.46 (d, $J = 5.7$ Hz, 2H), 2.77 (q, $J = 6.4$ Hz, 3H), 2.56 (d, $J = 11.7$ Hz, 2H), 2.44 (ddd, $J = 12.5, 8.6, 3.6$ Hz, 2H), 2.34 (s, 1H), 2.18 (dt, $J = 26.2, 9.5$ Hz, 2H), 1.99 – 1.81 (m, 5H), 1.71 (d, $J = 12.6$ Hz, 1H), 1.37 – 1.18 (m, 2H), 1.03 – 0.80 (m, 9H). LCMS (ESI ⁺): m/z 563.5 [M+H] ⁺ .
107		(S)-1-(2-fluoro-5-((4-((4-fluoro-1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dio

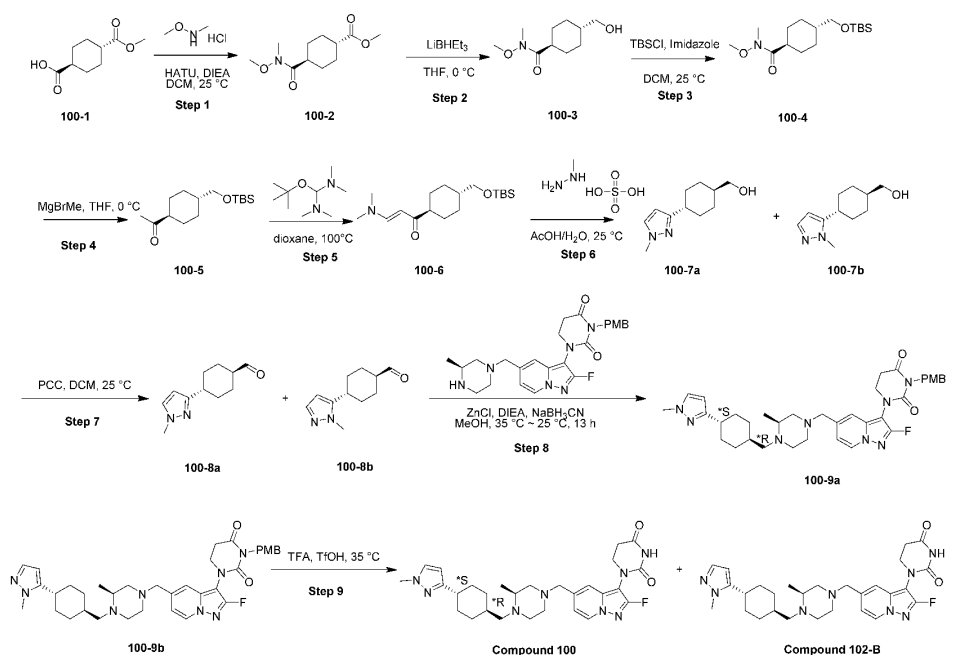
		ne, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.52 (s, 1H), 8.50 (d, $J = 7.1$ Hz, 1H), 7.66 (d, $J = 4.7$ Hz, 1H), 7.48 (s, 1H), 6.95 (dd, $J = 7.1, 1.8$ Hz, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.68 (d, $J = 4.2$ Hz, 3H), 3.52 – 3.41 (m, 2H), 2.78 (t, $J = 6.7$ Hz, 3H), 2.66 – 2.53 (m, 3H), 2.33 (s, 2H), 1.89 (dd, $J = 22.4, 12.2$ Hz, 5H), 1.73 (d, $J = 13.3$ Hz, 2H), 1.45 (dt, $J = 17.9, 12.4$ Hz, 3H), 1.24 (d, $J = 5.3$ Hz, 1H), 0.97 (d, $J = 21.9$ Hz, 5H). LCMS (ESI^+): m/z 555.7 $[\text{M}+\text{H}]^+$.
108		(S)-1-(2-fluoro-5-((3-methyl-4-((4-(2-methylpyrimidin-5-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.52 (s, 1H), 8.59 – 8.47 (m, 3H), 7.48 (s, 1H), 6.96 (dd, $J = 7.2, 1.8$ Hz, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.53 – 3.40 (m, 2H), 2.84 – 2.72 (m, 3H), 2.67 – 2.30 (m, 7H), 2.26 – 2.12 (m, 2H), 2.02 – 1.89 (m, 3H), 1.85 – 1.70 (m, 3H), 1.60 – 1.29 (m, 4H), 1.10 – 0.82 (m, 5H). LCMS (ESI^+): m/z 549.7 $[\text{M}+\text{H}]^+$.
109		(S)-1-(5-((4-((4-(1-ethyl-1H-pyrazol-3-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.52 (s, 1H), 8.50 (d, $J = 7.1$ Hz, 1H), 7.60 – 7.44 (m, 2H), 6.96 (dd, $J = 7.1, 1.8$ Hz, 1H), 5.98 (d, $J = 2.2$ Hz, 1H), 4.02 (q, $J = 7.3$ Hz, 2H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.53 – 3.39 (m, 2H), 2.78 (t, $J = 6.7$ Hz, 3H), 2.64 – 2.28 (m, 4H), 2.26 – 2.09 (m, 2H), 2.00 – 1.59 (m, 6H), 1.54 – 1.20 (m, 7H), 1.09 – 0.81 (m, 5H). LCMS (ESI^+): m/z 551.5 $[\text{M}+\text{H}]^+$.

Example 25: preparation of compound 100

1-(2-fluoro-5-(((S)-3-methyl-4-(((1*r*,4*S*)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; and compound 102-B

1-(2-fluoro-5-(((S)-3-methyl-4-(((1*r*,4*S*)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methyl

yl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



Step 1: Synthesis of methyl

5 (1r,4r)-4-(methoxy(methyl)carbamoyl)cyclohexane-1-carboxylate

A mixture of (1r,4r)-4-(methoxycarbonyl)cyclohexane-1-carboxylic acid (10 g, 53.7 mmol), HATU (24.5 g, 64.4 mmol), DIEA (13.9 g, 107.4 mmol) and N,O-dimethylhydroxylamine hydrochloride (6.28 g, 64.4 mmol) in DCM (150 mL) was stirred at 25 °C for 2 hrs. The mixture was diluted with H₂O (200 mL), extracted with EA (200 mLx2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure give a residue, which was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum ether/Ethyl acetate @100 ml/min). Compound methyl (1r,4r)-4-(methoxy(methyl)carbamoyl)cyclohexane-1-carboxylate (7.0 g, 57% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 230.4 [M+H]⁺.

Step 2: Synthesis of

(1r,4r)-4-(hydroxymethyl)-N-methoxy-N-methylcyclohexane-1-carboxamide

A mixture of methyl (1r,4r)-4-(methoxy(methyl)carbamoyl)cyclohexane-1-carboxylate (3 g, 0.69 mmol) in THF (30 mL) was added LiBHET₃ at 0 °C, the mixture was stirred for 2 hrs at 0 °C. The reaction was quenched with aq. NH₄Cl (30 mL), extracted with EA (30 mLx2). The

combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure give a residue, which was used the next step directly. Compound (1*r*,4*r*)-4-(hydroxymethyl)-N-methoxy-N-methylcyclohexane-1-carboxamide (2.64 g, crude) was obtained as a colorless oil. LCMS (ESI⁺): m/z 202.2 [M+H]⁺.

5 **Step 3: Synthesis of**

(1*r*,4*r*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-N-methoxy-N-methylcyclohexane-1-carboxamide

A mixture of (1*r*,4*r*)-4-(hydroxymethyl)-N-methoxy-N-methylcyclohexane-1-carboxamide (2.64 g, 13.1 mmol), imidazole (1.34 g, 19.7 mmol), TBSCl (2.57 g, 17 mmol) in DCM (30 mL) was stirred at 25 ° C for 0.5 hr. The mixture was filtered and concentrated under reduced pressure give a residue, which was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~15% Petroleum ether/Ethyl acetate @50 ml/min). Compound (1*r*,4*r*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-N-methoxy-N-methylcyclohexane-1-carboxamide (2.25 g, 54% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 316.3 [M+H]⁺.

Step 4: Synthesis of

1-((1*r*,4*r*)-4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)ethan-1-one

A mixture of (1*r*,4*r*)-4-(((tert-butyldimethylsilyl)oxy)methyl)-N-methoxy-N-methylcyclohexane-1-carboxamide (2.25 g, 7.13 mmol) in THF (30 mL) was added MgBrMe (3.1 mL, 9.27mmol, 3M), the mixture was stirred at 0 ° C for 3 hrs. The mixture was quenched with NH₄Cl (aq, 30 mL), extracted with EA (30 mLx2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure give a residue, which was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum ether/Ethyl acetate @40 ml/min). Compound 1-((1*r*,4*r*)-4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)ethan-1-one (1.7 g, 88% yield) was obtained as a colorless oil.

30 **Step 5: Synthesis of**

(E)-1-((1*r*,4*r*)-4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)-3-(dimethylamino)prop-2-en-1-one

A mixture of 1-((1*r*,4*r*)-4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)ethan-1-one (1.7 g, 6.28

mmol), 1-tert-butoxy-N,N,N',N'-tetramethylmethanediamine (2.2 g, 12.6 mmol), in dioxane (20 mL) was stirred at 100 ° C for 5 hrs. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 15~30% Petroleum ether/Ethyl acetate @50 ml/min). Compound (E)-1-((1r,4r)-4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)-3-(dimethylamino)prop-2-en-1-one (1.4 g, 68% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 326.3 [M+H]⁺.

Step 6: Synthesis of ((1r,4r)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methanol and ((1r,4r)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methanol

A mixture of (E)-1-((1r,4r)-4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)-3-(dimethylamino)prop-2-en-1-one (1.4 g, 4.3 mmol), 1-tert-butoxy-N,N,N',N'-tetramethylmethanediamine (930 mg, 6.45 mmol), in AcOH (10 mL) and H₂O (10 mL) was stirred at 25 ° C for 2 hrs. The mixture was quenched with NaHCO₃ to adjust pH to 8, extracted with EA. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure give a residue, which was used the next step directly. The mixture of compound ((1r,4r)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methanol and ((1r,4r)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methanol (460 mg, crude) was obtained as a colorless oil.

LCMS (ESI⁺): m/z 195.1 [M+H]⁺.

Step 7: Synthesis of (1r,4r)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexane-1-carbaldehyde and (1r,4r)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexane-1-carbaldehyde

A mixture of ((1r,4r)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methanol and ((1r,4r)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methanol (460 mg, 2.37 mmol), PCC (765 mg, 3.55 mmol), in DCM (10 mL) was stirred at 25 ° C for 2 hrs. The mixture was filtered and concentrated under reduced pressure give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 20% Petroleum ether/Ethyl acetate @36 ml/min). the mixture of compound (1r,4r)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexane-1-carbaldehyde and (1r,4r)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexane-1-carbaldehyde was 300 mg, yield was 65% as a colorless oil. LCMS (ESI⁺): m/z 193.2 [M+H]⁺.

Step 8: Synthesis of

1-(2-fluoro-5-(((S)-3-methyl-4-(((1r,4S)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione and

1-(2-fluoro-5-(((S)-3-methyl-4-(((1r,4S)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione

A mixture of

(S)-1-(2-fluoro-5-(((S)-3-methyl-4-(((1r,4S)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (150 mg, 0.31 mmol),
10 (1r,4r)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexane-1-carbaldehyde and
(1r,4r)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexane-1-carbaldehyde (150 mg, 0.78 mmol)
and DIEA (124 mg, 0.92 mmol) in MeOH (6 mL) was stirred for 10 min at the room
temperature. ZnCl₂ (1 mL, 1 mmol, 1 M) was added, the mixture was stirred overnight at
room temperature. Then sodium cyanoborohydride (39 mg, 0.62 mmol) was added, the
15 reaction mixture was stirred for 1 hr at room temperature. The mixture was concentrated
under reduced pressure to give a residue, which was purified by flash silica gel
chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10%
DCM/MeOH @36 ml/min). The mixture of compound
1-(2-fluoro-5-(((S)-3-methyl-4-(((1r,4S)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)
20 piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidin
e-2,4(1H,3H)-dione and
1-(2-fluoro-5-(((S)-3-methyl-4-(((1r,4S)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methyl)
piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidin
e-2,4(1H,3H)-dione (150 mg, 74% yield) was obtained as a yellow oil. LCMS (ESI⁺): m/z
25 657.5 [M+H]⁺.

Step 9: Synthesis of

1-(2-fluoro-5-(((S)-3-methyl-4-(((1*r,4*S)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione

A mixture of

1-(2-fluoro-5-(((S)-3-methyl-4-(((1r,4S)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)
piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidin
e-2,4(1H,3H)-dione and
1-(2-fluoro-5-(((S)-3-methyl-4-(((1r,4S)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methyl)
35 piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidin

e-2,4(1H,3H)-dione (150 mg, 0.228 mmol), TfOH (3 mL) in TFA (3 mL) was stirred for 1 hr at 30 ° C. The reaction was quenched with aq. NaHCO₃ (30 mL), extracted with EA (20 mLx2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure give a residue, which was purified by

5 prep-HPLC (TFA). compound **100**:

1-(2-fluoro-5-(((S)-3-methyl-4-(((1*r*,4*S*)-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (38 mg, 31% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.55 (s, 1H), 8.57 (d, *J* = 7.1 Hz, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 6.98 (dd, *J* = 7.1, 1.9 Hz, 1H), 6.00 (d, *J* = 2.2 Hz, 1H), 3.75 (d, *J* = 5.1 Hz, 5H), 3.67 (s, 4H), 3.17 (s, 3H), 2.97 (s, 3H), 2.80 (t, *J* = 6.7 Hz, 3H), 2.38 (s, 1H), 2.00 – 1.87 (m, 3H), 1.74 (d, *J* = 11.5 Hz, 2H), 1.45 – 1.34 (m, 2H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.19 – 1.02 (m, 2H). LCMS (ESI⁺): *m/z* 537.5 [M+H]⁺.

Chiral analysis: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO₂-EtOH]; B:40%, isocratic elution mode; A/B = 1/1 at 1.0 mL/ min; Temp: 35 °C; Wavelength: 254 nm. Purity, 90.82%, RT=0.95 min.

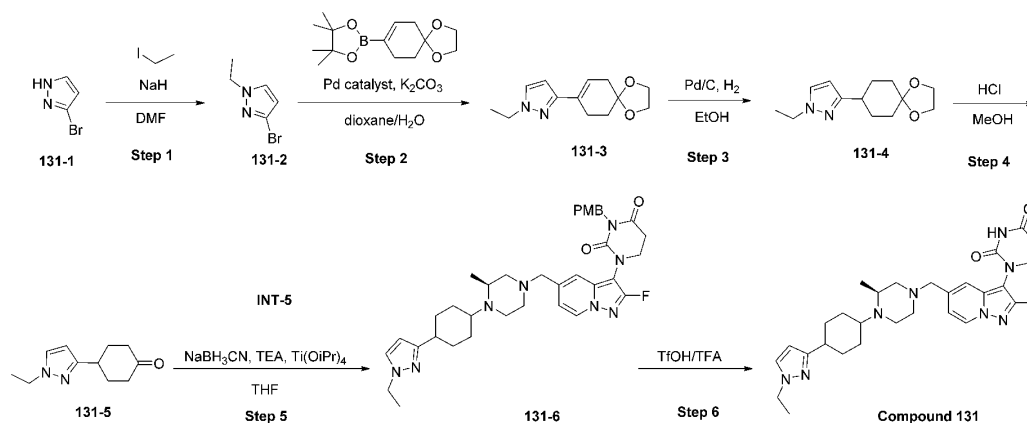
Compound 102-B:

1-(2-fluoro-5-(((S)-3-methyl-4-(((1*r*,4*S*)-4-(1-methyl-1H-pyrazol-5-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (62 mg, 51% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.55 (s, 1H), 8.57 (d, *J* = 7.1 Hz, 1H), 7.54 (s, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 6.98 (dd, *J* = 7.2, 1.9 Hz, 1H), 5.99 (d, *J* = 1.8 Hz, 1H), 3.75 (d, *J* = 3.4 Hz, 5H), 3.68 (s, 4H), 2.98 (d, *J* = 12.0 Hz, 2H), 2.80 (t, *J* = 6.7 Hz, 3H), 2.63 (dt, *J* = 11.7, 3.3 Hz, 2H), 2.37 (s, 1H), 2.00 – 1.85 (m, 3H), 1.78 (s, 2H), 1.49 – 0.93 (m, 7H). LCMS (ESI⁺): *m/z* 537.5 [M+H]⁺.

Chiral analysis: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase: [CO₂-EtOH]; B:40%, isocratic elution mode; A/B = 1/1 at 1.0 mL/ min; Temp: 35 °C; Wavelength: 254 nm.

Example 26: preparation of compound 131:

30 (S)-1-(5-((4-(4-(1-ethyl-1H-pyrazol-3-yl)cyclohexyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



Step 1: Synthesis of 3-bromo-1-ethyl-1H-pyrazole

To a solution of 3-bromo-1H-pyrazole (2 g, 13.61 mmol) in DMF (6 mL) was added NaH (653 mg, 60% in mineral oil). The reaction mixture was stirred at 25 °C for 30 min. Then iodoethane was added to the mixture. The mixture was stirred at rt for 2 hrs. The reaction was quenched by addition of water. The mixture was extracted with EA (50 mL). The organic layer was washed with brine (30 mLx3), dried over Na₂SO₄, filtered and concentrated to give a crude, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 1-6% Petroleum ether/Ethyl acetate @36 ml/min). Compound 3-bromo-1-ethyl-1H-pyrazole (1.63 g, 68% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 175.2 [M+H]⁺.

Step 2: Synthesis of 1-ethyl-3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-pyrazole

A mixture of 3-bromo-1-ethyl-1H-pyrazole (1.53 g, 8.74 mmol), 1,4-dioxaspiro[4.5]dec-7-en-8-boronic acid pinacol ester (2.33 g, 8.74 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (710 mg, 0.87 mmol), K₂CO₃ (2.42 g, 17.48 mmol) in dioxane/H₂O (20 mL/5 mL) was stirred under nitrogen atmosphere at 100 °C for 3 hrs. The mixture was extracted with EA (40 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 1-20% Petroleum ether/Ethyl acetate @60 ml/min). Compound 1-ethyl-3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-pyrazole (1.83 g, 89% yield) was obtained as a yellow oil. LCMS (ESI⁺): m/z 235.3 [M+H]⁺.

Step 3: Synthesis of 1-ethyl-3-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole

To a solution of 1-ethyl-3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-pyrazole (400 mg, 1.71 mmol) in EtOH (10 mL) was added 10% Pd/C (100 mg, wetted with 55% H₂O). The reaction mixture was stirred under hydrogen atmosphere at 40 °C for 3 hrs. The mixture was filtered through celite pad. The filtrate was concentrated to give a yellow oil (395 mg, 98%). LCMS (ESI⁺): m/z 237.4 [M+H]⁺.

Step 4: Synthesis of 4-(1-ethyl-1H-pyrazol-3-yl)cyclohexan-1-one

To a solution of 1-ethyl-3-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole (395 mg, 1.18 mmol) in ketone (7 mL) was added 6 N HCl aqueous solution (7 mL). The reaction mixture was stirred at 50 °C overnight. Saturated NaHCO₃ aqueous solution was added dropwise to the mixture to adjust the pH of the mixture to 7-8. The mixture was extracted with EA (30 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give a crude, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 1-25% Petroleum ether/Ethyl acetate @36 ml/min). Compound 4-(1-ethyl-1H-pyrazol-3-yl)cyclohexan-1-one (129 mg, 57% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 193.4 [M+H]⁺.

Step 5: Synthesis of

(S)-1-(5-((4-(4-(1-ethyl-1H-pyrazol-3-yl)cyclohexyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

To a solution of 4-(1-ethyl-1H-pyrazol-3-yl)cyclohexan-1-one (41 mg, 0.213 mmol) and INT-5 (100 mg, 0.193 mmol) in DCM (5 mL) was added TEA (78 mg, 0.772 mmol). The mixture was stirred at rt for 10 min. The volatiles were removed under reduced pressure to give a residue, which was dissolved in THF (5 mL). Ti(OiPr)₄ (165 mg, 0.579 mmol) was added to the solution. The mixture was stirred at 50 °C for 1 hr. Then NaBH₃CN (24 mg, 0.386 mmol) was added to the mixture. The reaction mixture was stirred at rt for 3 hrs. The mixture was concentrated under reduced pressure to give a residue, which was dissolved in EA (10 mL). The solution was washed with brine, dried over Na₂SO₄, filtrated and the volatiles were removed under reduced pressure to give a crude, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 1-5% DCM/MeOH @35 ml/min). Compound (S)-1-(5-((4-(4-(1-ethyl-1H-pyrazol-3-yl)cyclohexyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dio

ne (60 mg, 47% yield) was obtained as a yellow solid. LCMS (ESI⁺): m/z 657.7 [M+H]⁺.

Step 6: Synthesis of

(S)-1-(5-((4-(4-(1-ethyl-1H-pyrazol-3-yl)cyclohexyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

5 A mixture of

(S)-1-(5-((4-(4-(1-ethyl-1H-pyrazol-3-yl)cyclohexyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (60 mg, 0.091 mmol) in TFA /TfOH (2 mL/2 mL) was stirred at 35 °C for 1 hr. A saturated NaHCO₃ aqueous solution was added to the reaction to adjust the pH of the mixture to 7-8. The solution was extracted with EA (30 mL). The organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (FA condition).

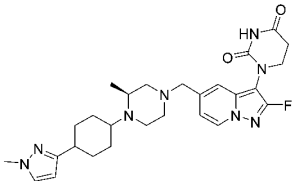
(S)-1-(5-((4-(4-(1-ethyl-1H-pyrazol-3-yl)cyclohexyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (7.81 mg, 16%

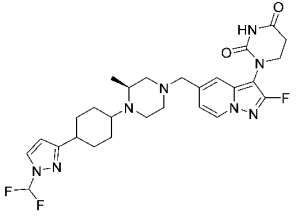
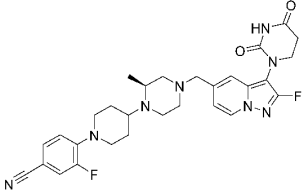
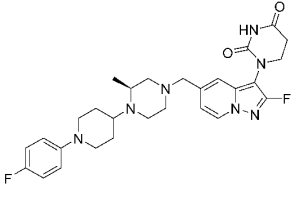
15 yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.54 (d, *J* = 3.5 Hz, 1H), 8.52 (dd, *J* = 7.2, 4.0 Hz, 1H), 7.61 – 7.45 (m, 2H), 6.96 (td, *J* = 7.4, 1.8 Hz, 1H), 6.04 (dd, *J* = 25.0, 2.2 Hz, 1H), 4.09 – 3.98 (m, 2H), 3.74 (td, *J* = 6.6, 4.3 Hz, 2H), 3.59 – 3.45 (m, 2H), 2.99 – 1.93 (m, 11H), 1.80 – 1.21 (m, 8H), 1.15 – 1.00 (m, 3H), 0.94 – 0.80 (m, 3H). LCMS (ESI⁺): m/z 537.6 [M+H]⁺.

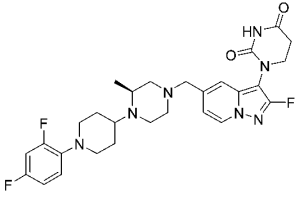
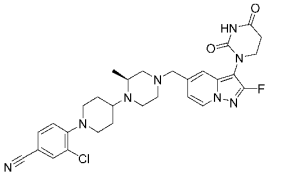
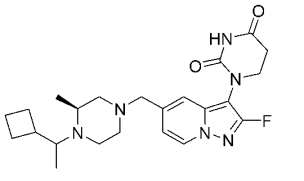
20

Example 27: The following compounds in **Table 10** were prepared according to the procedures described for the **Compound 131** using the appropriate ketone derivatives.

Table 10

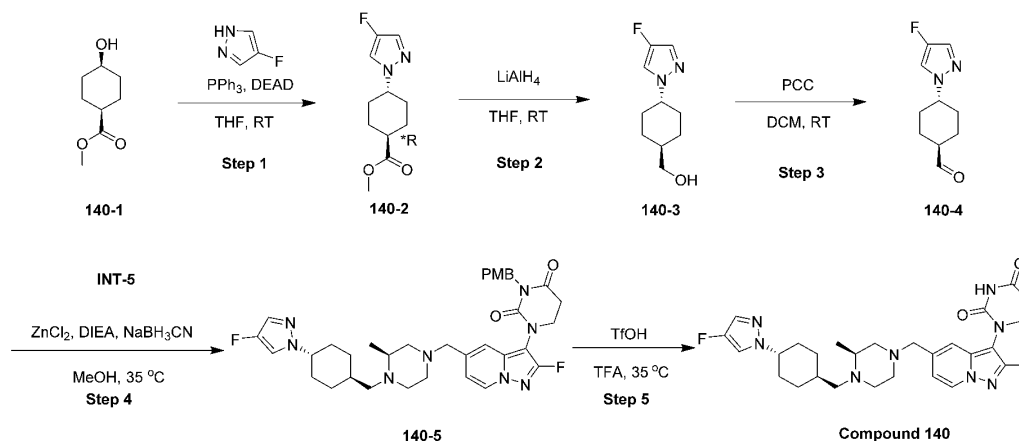
No.	Structure	Compound name and characterization
132		(S)-1-(2-fluoro-5-((3-methyl-4-(4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.52 (s, 1H), 8.50 (d, <i>J</i> = 7.0 Hz, 1H), 7.50 (d, <i>J</i> = 21.4 Hz, 2H), 6.95 (dd, <i>J</i> = 7.1, 1.8 Hz, 1H), 6.05 (s, 1H), 3.93 – 3.62 (m, 5H), 3.47 (s, 2H), 2.78 (t, <i>J</i> = 6.7 Hz, 3H), 2.63 (s, 1H), 2.42 (s, 4H), 2.03 (s, 3H), 1.82 – 0.76 (m, 10H). LCMS (ESI ⁺): m/z 523.58 [M+H] ⁺ .

133		(S)-1-(5-((4-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohexyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO-d_6) δ 10.52 (d, $J = 4.0$ Hz, 1H), 8.50 (dd, $J = 7.2, 4.1$ Hz, 1H), 8.22 (s, 1H), 8.08 (dd, $J = 14.2, 2.6$ Hz, 1H), 7.70 (td, $J = 59.4, 10.6$ Hz, 1H), 7.47 (d, $J = 8.5$ Hz, 1H), 6.95 (td, $J = 7.0, 1.8$ Hz, 1H), 6.39 (dd, $J = 9.0, 2.7$ Hz, 1H), 3.74 (td, $J = 6.6, 4.4$ Hz, 2H), 3.53 – 3.36 (m, 2H), 2.93 – 2.57 (m, 6H), 2.49 – 2.28 (m, 3H), 2.22 – 1.78 (m, 4H), 1.75 – 1.17 (m, 6H), 0.98 (d, $J = 6.2$ Hz, 3H). LCMS (ESI$^+$): m/z 559.4 $[\text{M}+\text{H}]^+$.
134		(S)-4-(4-(4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)piperidin-1-yl)-3-fluorobenzonitrile; ^1H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.53 (d, $J = 7.1$ Hz, 1H), 7.68 (dd, $J = 13.4, 1.9$ Hz, 1H), 7.56 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.51 (s, 1H), 7.14 (t, $J = 8.8$ Hz, 1H), 6.98 (dd, $J = 7.3, 1.8$ Hz, 1H), 3.76 (t, $J = 6.7$ Hz, 2H), 3.67 – 3.15 (m, 6H), 3.06 – 2.76 (m, 5H), 2.70 – 2.55 (m, 3H), 2.35 – 2.23 (m, 1H), 2.13 – 2.01 (m, 1H), 1.89 – 1.66 (m, 3H), 1.60 – 1.47 (m, 1H), 1.07 (d, $J = 6.2$ Hz, 3H). LCMS (ESI$^+$): m/z 563.5 $[\text{M}+\text{H}]^+$.
135		(S)-1-(2-fluoro-5-((4-(1-(4-fluorophenyl)piperidin-4-yl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ^1H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.54 (d, $J = 7.1$ Hz, 1H), 7.51 (s, 1H), 7.09 – 6.92 (m, 5H), 3.76 (t, $J = 6.7$ Hz, 2H), 3.67 (d, $J = 12.0$ Hz, 2H), 3.58 – 3.18 (s, 4H), 3.06 – 2.57 (m, 8H), 2.43 – 2.26 (m, 1H), 2.21 – 2.04 (m, 1H), 1.90 – 1.66 (m, 3H), 1.60 – 1.45 (m, 1H), 1.09 (d, $J = 6.2$ Hz, 3H). LCMS (ESI$^+$): m/z 538.5 $[\text{M}+\text{H}]^+$.

136		(S)-1-(5-((4-(1-(2,4-difluorophenyl)piperidin-4-yl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.56 (s, 1H), 8.53 (d, <i>J</i> = 7.1 Hz, 1H), 7.51 (s, 1H), 7.18 (ddd, <i>J</i> = 12.2, 8.9, 2.9 Hz, 1H), 7.12 – 7.03 (m, 1H), 7.02 – 6.94 (m, 2H), 3.76 (t, <i>J</i> = 6.7 Hz, 2H), 3.39 (s, 6H), 2.92 – 2.76 (m, 5H), 2.75 – 2.55 (m, 3H), 2.33 – 2.20 (m, 1H), 2.10 – 1.97 (m, 1H), 1.87 – 1.72 (m, 2H), 1.71 – 1.61 (m, 1H), 1.60 – 1.48 (m, 1H), 1.04 (d, <i>J</i> = 6.2 Hz, 3H). LCMS (ESI⁺): <i>m/z</i> 556.5 [M+H]⁺.
137		(S)-3-chloro-4-(4-(4-(((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)piperidin-1-yl)benzonitrile; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.56 (s, 1H), 8.54 (d, <i>J</i> = 7.1 Hz, 1H), 7.69 (dd, <i>J</i> = 13.4, 1.9 Hz, 1H), 7.56 (dd, <i>J</i> = 8.5, 2.0 Hz, 1H), 7.50 (s, 1H), 7.12 (t, <i>J</i> = 8.8 Hz, 1H), 6.95 (dd, <i>J</i> = 7.3, 1.8 Hz, 1H), 3.76 (t, <i>J</i> = 6.7 Hz, 2H), 3.67 – 3.15 (m, 6H), 3.06 – 2.76 (m, 5H), 2.70 – 2.55 (m, 3H), 2.35 – 2.23 (m, 1H), 2.13 – 2.01 (m, 1H), 1.89 – 1.66 (m, 3H), 1.60 – 1.47 (m, 1H), 1.07 (d, <i>J</i> = 6.2 Hz, 3H). LCMS (ESI⁺): <i>m/z</i> 579.4 [M+H]⁺.
138		1-(5-(((3S)-4-(1-cyclobutylethyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.57 (s, 1H), 8.55 (dd, <i>J</i> = 8 Hz, 1H), 7.52 (d, <i>J</i> = 4 Hz, 1H), 7.0 (t, <i>J</i> = 4 Hz, 1H), 3.78 - 3.74 (m, 2H), 3.2 - 3.1 (m, 2H), 2.8 - 2.7 (m, 2H), 2.62 - 2.55 (m, 2H), 2.43 - 2.32 (m, 3H), 2.28 - 2.11 (m, 2H), 2.02 - 1.84 (m, 3H), 1.78 - 1.62 (m, 2H), 1.30-1.20 (m, 3H), 1.14-1.0 (m, 4H), 0.96-0.85 (d, <i>J</i> = 6.4 Hz, 2H). LCMS (ESI⁺): <i>m/z</i> 443.5 [M+H]⁺.

Example 28: preparation of compound 140:

1-(2-fluoro-5-(((S)-4-(((1*r*,4*S*)-4-(4-fluoro-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione



5

Step 1: Synthesis of methyl**(1*r*,4*r*)-4-(4-fluoro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate**

A mixture of methyl (1*s*,4*s*)-4-hydroxycyclohexane-1-carboxylate (3.7 g, 23.2 mmol), 4-fluoro-1*H*-pyrazole (2.0 g, 23.2 mmol) and triphenylphosphine (9.1 g, 34.8 mmol) in THF (50 mL) was cooled to 0 °C. Diethyl azodicarboxylate (6.1 g, 34.8 mmol, dissolved in 20 mL THF) was added. The reaction mixture was stirred at 40 °C for 2 hrs. The reaction was quenched with H₂O (200 mL), extracted with EA (50 mLx2). The combined extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~15% Petroleum ether/Ethyl acetate @45 ml/min). Compound methyl (1*r*,4*r*)-4-(4-fluoro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (400 mg, 8% yield) was obtained as a white solid. LCMS (ESI⁺): *m/z* 227.3 [M+H]⁺.

15

Step 2: Synthesis of ((1*r*,4*r*)-4-(4-fluoro-1*H*-pyrazol-1-yl)cyclohexyl)methanol

A solution of methyl (1*r*,4*r*)-4-(4-fluoro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (400 mg, 1.8 mmol) in 10 mL THF was cooled to 0 °C. Lithium aluminum hydride (2.5*N*, 1.5 mL, 3.6 mmol) was added. The reaction mixture was stirred at 0 °C for 1 hr. The reaction was quenched with H₂O (100 mL), extracted with EA (50 mLx2). The combined extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g

25

SepaFlash® Silica Flash Column, Eluent of 0~50% Petroleum ether/Ethyl acetate @36 ml/min). Compound ((1r,4r)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)methanol (270 mg, 77% yield) was obtained as a white solid. LCMS (ESI⁺): m/z 199.3 [M+H]⁺.

Step 3: Synthesis of (1r,4r)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexane-1-carbaldehyde

5 To a solution of ((1r,4r)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)methanol (270 mg, 1.4 mmol) in 10 mL DCM was added pyridinium chlorochromate (442 mg, 2.1 mmol). The reaction mixture stirred at room temperature for 1 hr. The mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~20% Petroleum ether/Ethyl acetate @36 ml/min). Compound (1r,4r)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexane-1-carbaldehyde (167 mg, 63% yield) was obtained as a white solid. LCMS (ESI⁺): m/z 197.4 [M+H]⁺.

Step 5: Synthesis of

1-(2-fluoro-5-(((S)-4-(((1r,4S)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

A mixture of (S)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (100 mg, 0.21 mmol), (1r,4r)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexane-1-carbaldehyde (82 mg, 0.42 mmol) and DIEA (54 mg, 0.42 mmol) in MeOH (5 mL) was stirred at room temperature for 10 min. ZnCl₂ (0.5 mL, 1 mmol, 2 M in THF) was added, the mixture was stirred at room temperature overnight. Then sodium cyanoborohydride (27 mg, 0.42 mmol) was added, the reaction mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound 1-(2-fluoro-5-(((S)-4-(((1r,4S)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (100 mg, 73% yield) was obtained as a yellow oil. LCMS (ESI⁺): m/z 661.5 [M+H]⁺.

Step 6: Synthesis of

1-(2-fluoro-5-(((S)-4-(((1R,4S)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

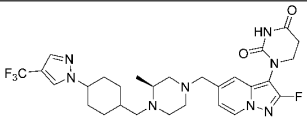
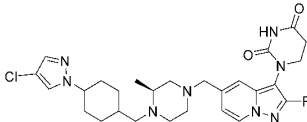
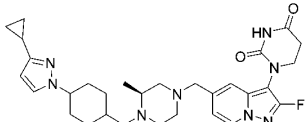
A mixture of

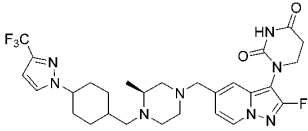
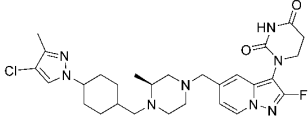
- 5 1-(2-fluoro-5-(((S)-4-(((1R,4S)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (100 mg, 0.15 mmol), TfOH (2.5 mL) in TFA (2.5 mL) was stirred at 30 °C for 1 hr. The reaction was quenched with aq. NaHCO₃ (30 mL), extracted with EA (15 mLx2). The combined extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound
- 10 1-(2-fluoro-5-(((S)-4-(((1R,4S)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (50 mg, 61% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.52 (s, 1H), 8.50 (d, *J* = 7.1 Hz, 1H), 7.86 (d, *J* = 4.5 Hz, 1H), 7.48 (s, 1H), 7.40 (d, *J* = 4.4 Hz, 1H), 6.95 (dd, *J* = 7.1, 1.8 Hz, 1H), 3.98 (ddt, *J* = 11.9, 7.8, 3.9 Hz, 1H), 3.74 (t, *J* = 6.7 Hz, 2H), 3.46 (d, *J* = 6.0 Hz, 2H), 2.77 (q, *J* = 6.0, 5.2 Hz, 3H), 2.56 (d, *J* = 10.2 Hz, 2H), 2.43 (dd, *J* = 12.4, 8.8 Hz, 1H), 2.39 – 2.31 (m, 1H), 2.19 (p, *J* = 9.4 Hz, 2H), 1.95 (t, *J* = 12.6, 7.4 Hz, 5H), 1.82 – 1.55 (m, 4H), 1.12 – 0.86 (m, 5H). LCMS (ESI⁺): *m/z* 541.4 [M+H]⁺.
- 20

Example 29: The following compounds in **Table 11** were prepared according to the procedures of the **compound 140**.

Table 11

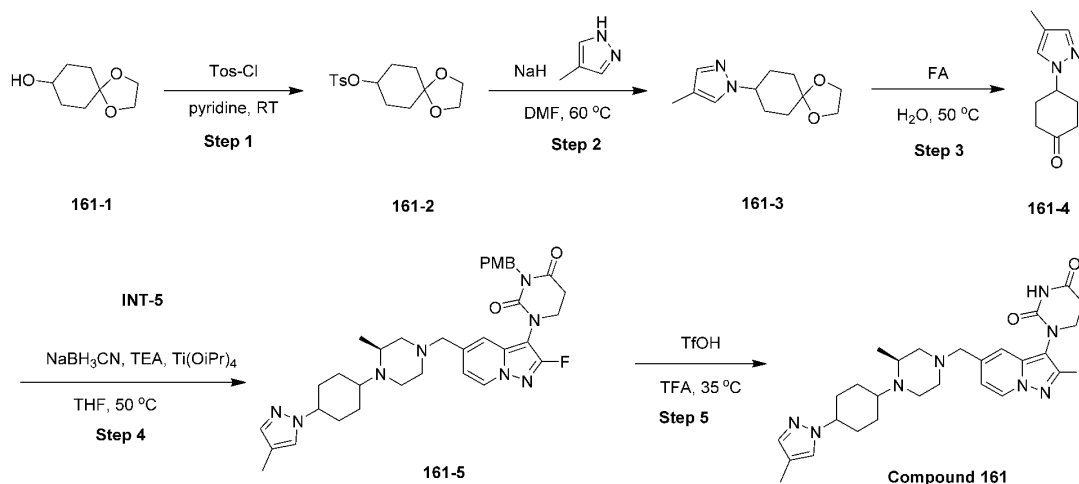
No.	Structure	Compound name and characterization
141		1-(2-fluoro-5-(((S)-4-(((1S,4R)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.54 (s, 1H), 8.53 (d, <i>J</i> = 7.1 Hz, 1H), 7.87 (d, <i>J</i> = 4.5 Hz, 1H), 7.51 (s, 1H), 7.41 (d, <i>J</i> = 4.4 Hz, 1H), 6.96 (dd, <i>J</i> = 7.2, 1.8 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.74 (t, <i>J</i> = 6.7 Hz, 3H), 3.56 (s, 2H), 2.79 (t, <i>J</i> =

		6.7 Hz, 4H), 2.00 (s, 4H), 1.71 (dd, $J = 34.4, 22.2$ Hz, 6H), 1.34 – 0.90 (m, 8H). LCMS (ESI ⁺): m/z 541.6 [M+H] ⁺ .
142		(S)-1-(2-fluoro-5-((3-methyl-4-((4-(4-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.52 (s, 1H), 8.50 (d, $J = 7.1$ Hz, 1H), 8.38 (s, 1H), 7.84 (s, 1H), 7.48 (s, 1H), 6.96 (dd, $J = 7.2, 1.8$ Hz, 1H), 4.23 – 4.11 (m, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.53 – 3.42 (m, 2H), 2.78 (t, $J = 6.7$ Hz, 3H), 2.57 (d, $J = 10.4$ Hz, 3H), 2.47 – 2.31 (m, 3H), 2.20 (p, $J = 9.8$ Hz, 2H), 2.09 – 1.90 (m, 5H), 1.74 (dt, $J = 18.3, 12.0$ Hz, 3H), 1.49 (s, 1H), 0.95 (d, $J = 6.1$ Hz, 3H). LCMS (ESI ⁺): m/z 591.3 [M+H] ⁺ .
143		1-(5-(((S)-4-(((1R,4S)-4-(4-chloro-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.52 (s, 1H), 8.50 (d, $J = 7.1$ Hz, 1H), 7.97 (s, 1H), 7.48 (d, $J = 2.9$ Hz, 2H), 6.95 (dd, $J = 7.2, 1.8$ Hz, 1H), 4.06 (ddt, $J = 11.9, 7.6, 3.8$ Hz, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.46 (d, $J = 5.9$ Hz, 4H), 2.77 (q, $J = 5.9, 5.1$ Hz, 3H), 2.56 (d, $J = 11.5$ Hz, 2H), 2.43 (dd, $J = 12.5, 8.9$ Hz, 1H), 2.35 (s, 1H), 2.19 (p, $J = 9.0, 8.2$ Hz, 2H), 2.04 – 1.88 (m, 5H), 1.80 – 1.59 (m, 3H), 1.52 – 1.41 (m, 1H), 0.94 (d, $J = 6.3$ Hz, 3H). LCMS (ESI ⁺): m/z 557.6 [M+H] ⁺ .
144		(S)-1-(5-((4-((3-cyclopropyl-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.52 (s, 1H), 8.50 (d, $J = 7.1$ Hz, 1H), 7.48 (s, 1H), 7.30 –

		7.10 (m, 2H), 6.96 (dd, $J = 7.2, 1.8$ Hz, 1H), 5.33 (dd, $J = 5.4, 4.1$ Hz, 2H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.60 – 3.42 (m, 2H), 2.79 (t, $J = 6.7$ Hz, 4H), 2.20 (t, $J = 11.7$ Hz, 2H), 2.12 – 1.92 (m, 6H), 1.92 – 1.73 (m, 5H), 1.61 – 1.39 (m, 4H), 1.10 – 0.72 (m, 4H), 0.58 (dd, $J = 5.1, 2.0$ Hz, 2H). LCMS (ESI ⁺): m/z 563.57 [M+H] ⁺ .
145		(S)-1-(2-fluoro-5-((3-methyl-4-((4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.46 (s, 1H), 8.44 (d, $J = 7.2$ Hz, 1H), 7.92 (s, 1H), 7.42 (s, 1H), 6.89 (dd, $J = 7.2, 1.8$ Hz, 1H), 6.62 (d, $J = 2.4$ Hz, 1H), 4.21 – 4.11 (m, 1H), 3.67 (t, $J = 6.7$ Hz, 2H), 3.49 – 3.36 (m, 2H), 2.93 – 2.76 (m, 1H), 2.72 (t, $J = 6.7$ Hz, 2H), 2.65 – 2.12 (m, 5H), 2.09 – 1.84 (m, 5H), 1.81 – 1.42 (m, 5H), 1.15 – 0.81 (m, 5H). LCMS (ESI ⁺): m/z 591.6 [M+H] ⁺ .
146		(S)-1-(5-((4-((4-(4-chloro-3-methyl-1H-pyrazol-1-yl)cyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione, ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.45 (s, 1H), 8.43 (d, $J = 7.5$ Hz, 1H), 7.79 (s, 0.6H), 7.41 (s, 1H), 7.37 (s, 0.4H), 6.88 (dd, $J = 7.2, 1.8$ Hz, 1H), 4.06 – 3.85 (m, 1H), 3.67 (t, $J = 6.7$ Hz, 2H), 3.46 – 3.31 (m, 2H), 2.71 (t, $J = 6.7$ Hz, 3H), 2.61 – 2.00 (m, 8H), 1.98 – 1.78 (m, 5H), 1.80 – 1.31 (m, 5H), 1.06 – 0.82 (m, 5H). LCMS (ESI ⁺): m/z 571.6 [M+H] ⁺ .

Example 30: Preparation of compound 161:

(S)-1-(2-fluoro-5-((3-methyl-4-(4-(4-methyl-1H-pyrazol-1-yl)cyclohexyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



Step 1: Synthesis of 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate

To a solution of 1,4-dioxaspiro[4.5]decan-8-ol (1000 mg, 6.3 mmol) in 8 mL pyridine was added Tos-Cl (1450 mg, 7.6 mmol). The reaction mixture was stirred at room temperature for 5 hrs. The reaction was poured into 30 mL H₂O, and extracted with EA. The organic layer was washed with 1 N HCl aqueous solution (50 mL) and brine successively, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum ether/Ethyl acetate @40 ml/min). Compound 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate (1.06 g, 54% yield) was obtained as a white solid.

Step 2: Synthesis of 4-methyl-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole

To a solution of 4-methyl-1H-pyrazole (55 mg, 0.7 mmol) in 5 mL DMF was added NaH (27 mg, 0.7 mmol). The reaction mixture was stirred at 25 °C for 30 min. Then 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate (200 mg, 0.6 mmol) was added. The reaction mixture was stirred at 60 °C for 5 hrs. The reaction was quenched with H₂O (30 mL), extracted with EA (20 mL x 2). The combined extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~15% Petroleum ether/Ethyl acetate @36 ml/min). Compound 4-methyl-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole (71 mg, 50% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 223.4 [M+H]⁺.

Step 3: Synthesis of 4-(4-methyl-1H-pyrazol-1-yl)cyclohexan-1-one

A mixture of 4-methyl-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole (70 mg, 0.3 mmol), TFA (3 mL) in H₂O (1 mL) was stirred at 50 °C for 1 hr. The reaction was quenched with aq. NaHCO₃ (20 mL), extracted with EA (15 mL x 2). The combined extracts were washed with brine dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum ether/Ethyl acetate @36 ml/min). Compound 4-(4-methyl-1H-pyrazol-1-yl)cyclohexan-1-one (40 mg, 71% yield) was obtained as a colorless oil. LCMS (ESI⁺): m/z 179.3 [M+H]⁺.

Step 4: Synthesis of

10 (S)-1-(2-fluoro-5-((3-methyl-4-(4-(4-methyl-1H-pyrazol-1-yl)cyclohexyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

To a solution of 4-(4-methyl-1H-pyrazol-1-yl)cyclohexan-1-one (40 mg, 0.21 mmol) and INT-5 (100 mg, 0.20 mmol) in DCM (5 mL) was added TEA (78 mg, 0.772 mmol). The mixture was stirred at rt for 10 min. The volatiles were removed under reduced pressure to give a residue, which was dissolved in THF (5 mL). Ti(OiPr)₄ (165 mg, 0.579 mmol) was added to the solution. The mixture was stirred at 50 °C for 1 hr. Then NaBH₃CN (24 mg, 0.386 mmol) was added to the mixture. The reaction mixture was stirred at rt for 3 hrs. The mixture was concentrated under reduced pressure to give a residue, which was dissolved in EA (10 mL). The solution was washed with brine, dried over Na₂SO₄, filtrated and the volatiles were removed under reduced pressure to give a crude, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound (S)-1-(2-fluoro-5-((3-methyl-4-(4-(4-methyl-1H-pyrazol-1-yl)cyclohexyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (80 mg, 60% yield) was obtained as a yellow oil. LCMS (ESI⁺): m/z 643.7 [M+H]⁺.

Step 5: Synthesis of

30 (S)-1-(2-fluoro-5-((3-methyl-4-(4-(4-methyl-1H-pyrazol-1-yl)cyclohexyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

A mixture of (S)-1-(2-fluoro-5-((3-methyl-4-(4-(4-methyl-1H-pyrazol-1-yl)cyclohexyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-

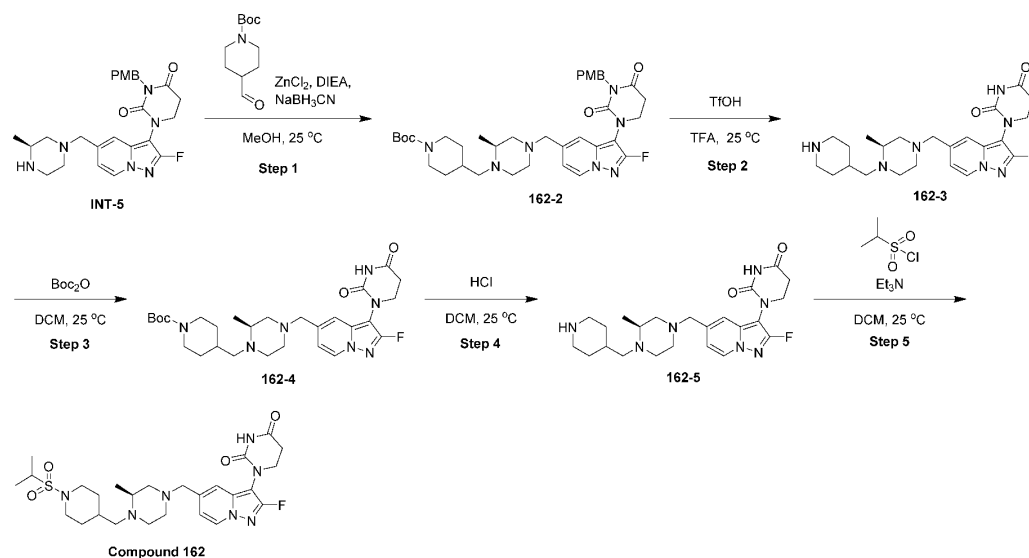
dione (80 mg, 0.1 mmol), TfOH (2.5 mL) in TFA (2.5 mL) was stirred at 30°C for 1 hr. The reaction was quenched with NaHCO₃ (aq, 30 mL), extracted with EA (15 mLx2). The combined extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel

5 chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound

(S)-1-(2-fluoro-5-((3-methyl-4-(4-(4-methyl-1H-pyrazol-1-yl)cyclohexyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione (37 mg, 54% yield) was obtained as a white solid. LCMS (ESI⁺): m/z 523.6 [M+H]⁺.

10

Example 31: Preparation of compound 162:
(S)-1-(2-fluoro-5-((4-((1-(isopropylsulfonyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione



15 **Step 1: Synthesis of tert-butyl**

(S)-4-((4-((2-fluoro-3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate

A mixture of

20 (S)-1-(2-fluoro-5-((3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)-3-(4-methoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (500 mg, 1.04 mmol), *tert*-butyl 4-formylpiperidine-1-carboxylate (333 mg, 1.56 mmol) and DIEA (268 mg, 2.08 mmol) in

MeOH (5 mL) was stirred at room temperature for 10 min. ZnCl₂ (1 mL, 2 mmol, 2 M in THF) was added, the mixture was stirred at room temperature overnight. Then sodium cyanoborohydride (131 mg, 2.08 mmol) was added, the reaction mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound tert-butyl (S)-4-((4-((2-fluoro-3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (470 mg, 67% yield) was obtained as a white solid. LCMS (ESI⁺): m/z 678.6 [M+H]⁺.

10 Step 2: Synthesis of

(S)-1-(2-fluoro-5-((3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

A mixture of tert-butyl

(S)-4-((4-((2-fluoro-3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (470 mg, 0.69 mmol), TfOH (2 mL) in TFA (2 mL) was stirred at 30 °C for 1 hr. The reaction was quenched with NaHCO₃ (aq, 30 mL), extracted with EA (20 mL*2), split, organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure give a colorless oil (300 mg, 95% yield), which was used into the next step without further purification. LCMS (ESI⁺): m/z 458.5 [M+H]⁺.

20 Step 3: Synthesis of tert-butyl

(S)-4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate

To a solution of

(S)-1-(2-fluoro-5-((3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (300 mg, 0.65 mmol) in 5 mL DCM was added di-*tert*-butyl dicarbonate (283 mg, 1.30 mmol). The reaction mixture was stirred at room temperature for 1 hr. The reaction was washed with H₂O (15 mL*2), organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound tert-butyl

(S)-4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (340 mg, 82% yield) was obtained as a white solid. LCMS (ESI⁺): m/z 558.5 [M+H]⁺.

Step 4: Synthesis of

5 (S)-1-(2-fluoro-5-((3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

A mixture of tert-butyl tert-butyl

(S)-4-((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate (340 mg, 0.61 mmol) and HCl (2N, 2 mL) was stirred at 25 °C for 1 hr. The reaction was concentrated under reduced pressure give a white solid (280 mg, 93% yield), which was used into the next step without further purification. LCMS (ESI⁺): m/z 458.4 [M+H]⁺.

Step 5: Synthesis of

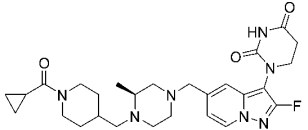
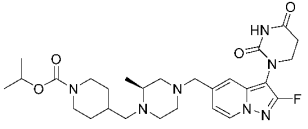
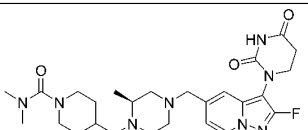
15 (S)-1-(2-fluoro-5-((4-((1-(isopropylsulfonyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

To a solution of

(S)-1-(2-fluoro-5-((3-methyl-4-(piperidin-4-ylmethyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (60 mg, 0.13 mmol) in 5 mL DCM was added Et₃N (39 mg, 0.39 mmol), followed by propane-2-sulfonyl chloride (19 mg, 0.13 mmol). The reaction mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% DCM/MeOH @36 ml/min). Compound
(S)-1-(2-fluoro-5-((4-((1-(isopropylsulfonyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (13 mg, 17% yield) was obtained as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.53 (d, *J* = 7.2 Hz, 1H), 6.63 (s, 1H), 6.20 (dd, *J* = 7.2, 1.9 Hz, 1H), 3.04 (t, *J* = 6.7 Hz, 2H), 2.98 (dq, *J* = 13.1, 2.4 Hz, 2H), 2.80 (d, *J* = 6.1 Hz, 2H), 2.48 – 2.39 (m, 2H), 2.21 – 1.85 (m, 9H), 1.68 (s, 2H), 1.48 (d, *J* = 11.3 Hz, 1H), 1.16 – 0.88 (m, 4H), 0.58 – 0.33 (m, 11H). LCMS
(ESI⁺): m/z 564.5 [M+H]⁺

Example 32: The following compounds in **Table 12** were prepared according to the procedures of the **compound 162**.

Table 12

No.	Structure	Compound name and Characterization
163		(S)-1-(5-(((4-((1-(cyclopropanecarbonyl)piperidin-4-yl)methyl)-3-methylpiperazin-1-yl)methyl)-2-fluoropyrazolo[1,5-a]pyridin-3-yl) dihydropyrimidine-2,4(1H,3H)-dione; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.54 (s, 1H), 8.51 (d, <i>J</i> = 7.1 Hz, 1H), 7.48 (s, 1H), 6.95 (dd, <i>J</i> = 7.2, 1.8 Hz, 1H), 4.27 (d, <i>J</i> = 38.1 Hz, 2H), 3.74 (t, <i>J</i> = 6.7 Hz, 2H), 3.48 (s, 2H), 3.19 – 2.95 (m, 2H), 2.78 (t, <i>J</i> = 6.7 Hz, 3H), 2.58 (s, 2H), 2.21 (s, 2H), 1.93 (hept, <i>J</i> = 5.1 Hz, 2H), 1.87 – 1.54 (m, 4H), 1.29 – 1.21 (m, 2H), 0.95 (s, 5H), 0.74 – 0.62 (m, 4H). LCMS (ESI⁺): <i>m/z</i> 526.5 [M+H]⁺
164		isopropyl (S)-4-(((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)piperidine-1-carboxylate; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.47 (s, 1H), 8.43 (dd, <i>J</i> = 7.2, 0.8 Hz, 1H), 7.48 – 7.34 (m, 1H), 6.88 – 6.85 (m, 1H), 4.67 (hept, <i>J</i> = 6.2 Hz, 1H), 3.86 (d, <i>J</i> = 12.3 Hz, 2H), 3.67 (t, <i>J</i> = 6.7 Hz, 3H), 3.40 (d, <i>J</i> = 4.5 Hz, 3H), 2.72 (t, <i>J</i> = 6.7 Hz, 3H), 2.67 – 2.46 (m, 4H), 2.42 – 2.36 (m, 1H), 2.31 (s, 1H), 2.13 (d, <i>J</i> = 8.1 Hz, 2H), 1.95 – 1.80 (m, 2H), 1.67 (d, <i>J</i> = 13.3 Hz, 1H), 1.53 (t, <i>J</i> = 13.2 Hz, 2H), 1.09 (d, <i>J</i> = 6.2 Hz, 6H), 0.87 (d, <i>J</i> = 6.2 Hz, 3H). LCMS (ESI⁺): <i>m/z</i> 544.5 [M+H]⁺
165		(S)-4-(((4-((3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoropyrazolo[1,5-a]pyridin-5-yl)methyl)-2-methylpiperazin-1-yl)methyl)-N,N-dimethylpiperidine-1-carboxamide; ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.54 (s, 1H), 8.51 (d, <i>J</i> = 7.1 Hz, 1H), 7.48 (s, 1H), 6.95 (dd, <i>J</i> = 7.2, 1.8 Hz, 1H), 3.74 (t, <i>J</i> = 6.7 Hz, 2H), 3.50 (dd, <i>J</i> = 13.0, 3.6 Hz, 4H), 2.93 – 2.85 (m, 1H), 2.78 (t, <i>J</i> = 6.7 Hz, 2H), 2.70 (s, 6H), 2.62 (t, <i>J</i> = 13.1, 8.1 Hz, 5H), 2.35 – 2.22 (m, 2H), 2.11 – 1.93 (m, 2H), 1.74

		(d, $J = 13.0$ Hz, 1H), 1.60 (t, $J = 14.8$ Hz, 2H), 1.24 (dd, $J = 7.4, 5.3$ Hz, 2H), 1.08 (td, $J = 12.3, 3.8$ Hz, 1H), 0.98 (d, $J = 6.2$ Hz, 3H). LCMS (ESI ⁺): m/z 529.4 [M+H] ⁺
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Example 51: WIZ protein degradation assay (HiBiT assay)

The following is an example of an assay that can be used to determine WIZ degradation activity of compounds in the HT-1080 cell line. HT-1080 cell line was purchased from ATCC (Cat# CCL-121), which was then engineered to stably overexpress GSPT (1-138)/G575N mutant and HiBiT tagged WIZ isoform 3. Cells were cultured in DMEM medium supplemented with 10% heat-inactivated FBS, 1X sodium pyruvate, 1X non-essential amino acids, 1X glutamine, 100 U/ml penicillin, and 100 ug/mL streptomycin. For WIZ degradation assay, about 10,000 engineered HT-1080 cells in 35 μ l culture medium were seeded into 384-well plates (Cat# 3764, Corning), pre-spotted with test compounds using the Echo 650 liquid handler (Beckman). The half-log dose-response-curve (DRC) typically has 10 points with the highest concentration at 10 μ M, and the lowest concentration at 0.316 nM. Assay plates were incubated at 37 $^{\circ}$ C with 5% CO₂ for 20 hrs. WIZ degradation was then assessed using the Nano-Glo HiBiT Lytic Detection Reagent according to the manufacturer's instructions. Luminescence was measured on a Pherastar microplate reader (BMG Labtech). The data was processed using Collaborative Drug Discovery Vault and DMSO control was used as the reference value to calculate degradation values for each treated sample (% compared to DMSO control). A four-Parameter Logistic Model was used to determine the compound's EC₅₀ and DC₅₀, using the following equation:

$$y = (A + ((B - A) / (1 + ((C/x)^D))))$$

A = Y_{min} (lowest WIZ level normalized to DMSO control in response to compound treatment, as determined by curve fit)

B = Y_{max} (highest value, WIZ value in DMSO control)

C = EC₅₀

25 D = Hill Slope

x = compound concentration

EC₅₀ = the concentration of compound when $y = (Y_{\max} - Y_{\min})/2$

DC₅₀ = the concentration of the sample when y = 50% of DMSO control (50% WIZ degradation)

y = WIZ protein level normalized to DMSO control

$$D_{\max} = (1 - Y_{\min}/Y_{\max}) * 100\%$$

$D_{\max}$ represented the maximum percentage of WIZ degradation that could be achieved by a compound at its highest treatment concentration. The results of compounds described in the present invention as well as three references are shown in Table 15.

Reference 1 is (S)-1-(5-((4-isobutyl-3-methylpiperazin-1-yl)methyl)pyrazolo

[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; **Reference 2** is

(S)-1-(5-((4-((4,4-difluorocyclohexyl)methyl)-3-methylpiperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione; **Reference 3** is

(S)-1-(5-((3-methyl-4-((tetrahydro-2H-pyran-4-yl)methyl)piperazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione. **Reference 1, 2, and 3** are

Example 203, Example 207 and Example 202, respectively, described in WO2022/195454.

Table 15 WIZ protein degradation activity

Compound No.	WIZ DC ₅₀ (nM)	WIZ D _{max} (%)
1	113	84.0
3	112	82.1
4	49.4	84.9
6	93.1	87.6
7	112	81.5
8	79.4	84.7
10	57.4	86.4
11	47.8	86.2
13	33.8	88.9
14	107	83.0
15	98.8	83.8
16	109	92.2
17	39.8	92.2
20	4670	58.5
21	112	81.2
22	681	79.9
23	125	81.2
24	143	80.6
25	130	83.4
26	248	74.6

27	98.9	83.3
30	230	78.5
31	124	81.2
32	854	74.0
33	224	80.4
34	51.7	31.6
35	30.5	81.0
37	198	81.4
38	426	79.5
39	85.7	90.9
40	59.7	90.6
41	130	87.0
42	92.1	91.3
43	118	87.9
44	197	82.5
45	183	90.4
46	119	91.7
47	109	92.2
48	33.3	90.6
49	127	87.5
51	1030	75.8
52	NA	40.7
53	15.6	93.8
54	20.1	91.6
55	13.7	95.0
56	16.6	93.0
57	10.3	94.9
58	15.5	92.5
59	15.7	93.4
60	11.7	92.4
61	10.7	92.3
62	22.6	92.3
63	15.8	92.9
64	11.2	92.8
65	15.4	94.0

66	22.7	93.3
67	31.1	90.1
69	24	93.7
70	21.6	91.0
71	9.8	95.0
72	7.4	94.5
73	10	94.9
74	11.9	92.7
75	9.6	91.6
76	21.9	92.3
77	37.8	90.6
78	22.3	92.0
79	34.8	93.5
80	19.8	92.3
81	29.5	93.7
82	24.9	93.4
85	32.9	90.1
86	17.5	92.9
87	33.6	92.5
88	28.3	93.1
89	24.6	93.7
90	23.8	93.4
91	36.0	90.5
92	47.8	89.3
93	53.6	89.8
94	48.9	90.2
95	17.1	93.4
96	11.7	95.6
97	22.5	93.5
98	13.7	93.1
99	15.9	93.4
100	26.5	91.3
101	19.9	92.0
102	40.1	90.2
102-B	2.4	94.3

103	57.4	92.0
104	11	94.6
105	30.4	90.5
106	6.7	94.1
107	10	94
108	17.9	92.1
109		
131	43.9	86.4
132	43.3	87.7
133	44.8	87.7
134	54.4	89.8
135	54.4	88.5
136	44.1	88.5
137	57.4	89.6
138	121	80.1
140	41.8	92.1
141	39.8	90.8
142	7.2	94
143	40.2	91.6
144	69.2	91.4
145	39	90
146	33.3	92
161	7.5	92.2
162	47.6	88.8
163	70.9	88.2
164	16.6	94.7
165	98.2	89.1
Reference 1	692	70.8
Reference 2	1340	72.4
Reference 3	521	72.6

Example 52**Fetal hemoglobin induction assay upon WIZ degradation**

Primary human CD34⁺ cells were purchased from STEMCELL Technologies Inc. The cells

were isolated from G-CSF mobilized peripheral blood leukapheresis samples obtained from healthy donors. Erythroid differentiation was performed using a 2-phase liquid culture system. During the first 6 days (first phase), cells were expanded in StemSpan™ SFEM II hematopoietic medium (STEMCELL Technologies Inc.) containing rhIL-3 (Peprotech, Inc.), rhIL-6 (Peprotech, Inc.), rhSCF (Peprotech, Inc.), rhFlt3L (Peprotech, Inc.), and antibiotic-antimycotic (Gibco™) at a density of 1×10^4 cells/mL. Cells were then differentiated toward the erythroid lineage (second phase) in IMDM (Gibco™) containing heparin (Millipore Sigma), human insulin (Millipore Sigma), human AB serum (Millipore Sigma), human holo-Transferrin (Millipore Sigma), hydrocortisone (STEMCELL Technologies Inc.), rhIL-3 (Peprotech, Inc.), rhEPO (Peprotech, Inc.), rhSCF (Peprotech, Inc.), and antibiotic-antimycotic (Gibco™) in the presence of test compounds for 7 days at a density of 5×10^3 cells/mL.

Fetal hemoglobin staining and flow cytometry

After 7 days of fetal hemoglobin induction upon erythroid differentiation, cells were washed and resuspended in stain buffer (BD Biosciences) supplemented with human FcR blocking reagent (Miltenyi Biotec) and incubated for 15 minutes at room temperature. The expression of erythroid markers was confirmed by staining with BV711-conjugated anti-CD71 (BD Biosciences), and APC-conjugated anti-CD235a (BD Biosciences) antibodies for 20 minutes at room temperature in the dark. To prepare the samples for fetal hemoglobin staining, the cells were first washed with stain buffer and treated with Cyto-Fast™ Fix/Perm buffer for 20 minutes at room temperature in the dark. Next, the cells were washed with Cyto-Fast™ Perm Wash solution and then stained with FITC-conjugated anti-HbF (Invitrogen) antibody for 30 minutes at room temperature in the dark. Finally, the cells were washed with Cyto-Fast™ Perm Wash solution and resuspended in stain buffer, followed by flow cytometry analysis using a NovoCyte Quanteon flow cytometer (Agilent). Data analysis was performed using the NovoExpress software (Agilent).

Table 16. HbF induction activity of compounds

Compound No.	HbF EC ₅₀ (nM)	HbF A _{max}
53	< 10	84.2%
54	< 10	87.8%
55	< 10	77.2%

Example 53: The pharmacokinetic study after single intravenous and oral

administration in mice

Sample collection and preparation: After intravenous injection or oral administration of test compounds, blood samples were collected and collection time was recorded. After collection, the blood sample was immediately transferred into a labeled centrifuge tube containing K2-EDTA, followed by centrifugation and plasma collection. The plasma was then transferred into a pre-cooled centrifuge tube, quickly frozen on dry ice, and stored in an ultra-low temperature refrigerator at -70±10°C until the LC-MS/MS analysis was performed.

Pharmacokinetic data analysis: The pharmacokinetic software was used to process the plasma drug concentration data of the compound in a non-compartmental model. The peak concentration (C_{max}), peak time (T_{max}) and quantifiable end time can be directly obtained from the plasma concentration-time diagram. The log-linear trapezoidal method was used to calculate the following pharmacokinetic parameters: half-life ($T_{1/2}$), apparent volume of distribution (V_{ss}) and clearance (Cl), and the area under the time-plasma concentration curve (AUC_{0-inf}) from the 0 point to the end point.

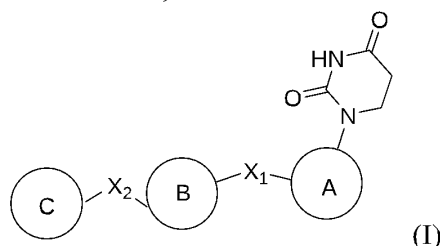
Table 17. Mouse PK profiles

Parameters		Compound 1	Compound 100	Reference 1
2 mg/kg, IV	CL (mL/min/kg)	21.3	22.7	52.4
	C_0 (ng/mL)	1325	2358	1469
	V_{ss} (L/kg)	2.99	1.5	2.10
10 mg/kg, PO	C_{max} (ng/mL)	1700	2513	944
	T_{max} (hr)	1.0	0.5	0.5
	$T_{1/2}$ (hr)	1.69	4.1	4.36
	$AUC_{(0-last)}$ (h*ng/mL)	5193	4806	1656
	F (%)	66.3	65.7	52.1

Conclusion from the pharmacokinetic study: compound 1 and compound 100 described in the present invention showed lower clearance rate, better oral exposure, and higher oral bioavailability than that of reference 1.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,

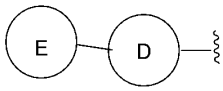


5 wherein:

X_1 and X_2 are each independently selected from the group consisting of a bond, $-(CH_2)_n-$, $-CH(R^1)(CH_2)_n-$, $-C(O)-$, and $-S(O)_2-$;

Ring A is independently selected from the group consisting of C_6 - C_{10} aryl, monocyclic 5- or 6-membered heteroaryl, bicyclic 9- or 10-membered heteroaryl, and
 10 tricyclic 12-, 13- or 14-membered heteroaryl, wherein the heteroaryl has 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N, wherein the aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^2 ;

Ring B is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 4 to
 15 10 membered monocyclic or bicyclic heterocyclyl, C_6 - C_{10} aryl, 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^3 ;

20 Ring C is independently selected from the group consisting of , C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_6 - C_{10} aryl-fused C_5 - C_{10} cycloalkyl, C_6 - C_{10} heteroaryl-fused C_5 - C_{10} cycloalkyl, C_6 - C_{10} aryl-fused 5 to 10-membered heterocyclyl, and C_6 - C_{10} heteroaryl-fused 5 to 10-membered heterocyclyl; wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are
 25 independently selected from the group consisting of O, S, and N; wherein the C_6 - C_{10} aryl-fused C_5 - C_{10} cycloalkyl, C_6 - C_{10} heteroaryl-fused C_5 - C_{10} cycloalkyl, C_6 - C_{10} aryl-fused 5 to 10-membered heterocyclyl, and C_6 - C_{10} heteroaryl-fused 5 to 10-membered heterocyclyl are optionally substituted with 1 to 6 identical or different substituents R^4 ;

Ring D is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 3 to
 30 8-membered heterocyclyl, C_6 - C_{10} aryl, and 5 to 10-membered heteroaryl, wherein the

heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R⁵;

5 Ring E is independently selected from the group consisting of absence, C₃-C₈ cycloalkyl, 3 to 8-membered heterocyclyl, C₆-C₁₀ aryl, and 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6
10 identical or different substituents R⁶;

wherein n is 0, 1, 2 or 3,

the H in -(CH₂)_n- can be optionally substituted with deuterium, C₁-C₆ alkyl, and halogen;

each R¹ is independently selected from the group consisting of H, deuterium, C₁-C₆
15 alkyl, and halogen;

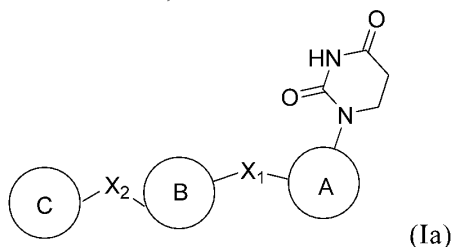
each R² is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

each R³ and R⁵ is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₆ alkanoyl, C₂-C₆ alkylester, C₁-C₆ thioalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, hydroxy C₁-C₆ alkyl, C₃-C₇ cycloalkyl, and 3 to 8-membered heterocyclyl, wherein the cycloalkyl, and heterocyclyl are optionally substituted with halogen, CN and -OMe;

each R⁴ and R⁶ is independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 3 to 8-membered heterocyclyl, nitro, amino, mercapto, -COOH, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₆ alkanoyl, C₂-C₆ alkylester, C₁-C₆ thioalkyl, hydroxyC₁-C₆ alkyl, aminoC₁-C₆ alkyl, (mono- and di-C₁-C₆ alkylamino)C₀-C₄ alkyl, -C₀-C₄ alkyl(C₃-C₇ cycloalkyl),
25 -O-C₀-C₄ alkyl(C₃-C₇ cycloalkyl), -C₀-C₄ alkyl-(phenyl), -C₀-C₄ alkylOC(O)OC₁-C₆ alkyl, -C₀-C₄ alkylOC(O)C₁-C₆ alkyl, -C₀-C₄ alkylC(O)OC₁-C₆ alkyl, C₀-C₄ alkyl-(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and C₀-C₄ alkyl-(5- or 6- membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, -C(O)OR⁷,
30 -C₀-C₄ alkylNR⁷R⁸, -C(O)NR⁷R⁸, -SO₂R⁷, -SO₂NR⁷R⁸, -OC(O)R⁷, and -C(NR⁷)NR⁷R⁸,

wherein R^7 and R^8 are independently chosen from hydrogen, C_1 - C_6 alkyl, $-C_0$ - C_4 alkyl(C_3 - C_7 cycloalkyl), and $-O$ - C_0 - C_4 alkyl(C_3 - C_7 cycloalkyl).

2. A compound of formula (Ia) or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,

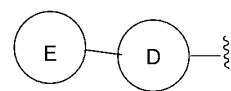


wherein:

X_1 and X_2 are each independently selected from the group consisting of a bond, $-(CH_2)_n-$, $-CH(R^1)(CH_2)_n-$, $-C(O)-$, and $-S(O)_2-$;

Ring A is independently selected from the group consisting of C_6 - C_{10} aryl, monocyclic 5- or 6-membered heteroaryl, bicyclic 9- or 10-membered heteroaryl, and tricyclic 12-, 13- or 14-membered heteroaryl, wherein the heteroaryl has 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N, wherein the aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^2 ;

Ring B is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C_6 - C_{10} aryl, 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R^3 ;



Ring C is independently selected from the group consisting of C_6 - C_{10} aryl-fused C_5 - C_7 cycloalkyl, C_6 - C_{10} heteroaryl-fused C_5 - C_7 cycloalkyl, C_6 - C_{10} aryl-fused 5 to 7-membered heterocyclyl, and C_6 - C_{10} heteroaryl-fused 5 to 7-membered heterocyclyl; wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are independently selected from the group consisting of O, S, and N; wherein the C_6 - C_{10} aryl-fused C_5 - C_7 cycloalkyl, C_6 - C_{10} heteroaryl-fused C_5 - C_7 cycloalkyl, C_6 - C_{10} aryl-fused 5 to 7-membered heterocyclyl, and C_6 - C_{10} heteroaryl-fused 5 to 7-membered heterocyclyl are optionally substituted with 1 to 6 identical or different substituents R^4 ;

Ring D is independently selected from the group consisting of C_3 - C_8 cycloalkyl, 3 to

8-membered heterocyclyl, C₆-C₁₀ aryl, and 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R⁵;

Ring E is independently selected from the group consisting of C₃-C₈ cycloalkyl, 3 to 8-membered heterocyclyl, C₆-C₁₀ aryl, and 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 6 identical or different substituents R⁶;

wherein n is 0, 1, 2 or 3,

the H in -(CH₂)_n- can be optionally substituted with deuterium, C₁-C₆ alkyl, and halogen;

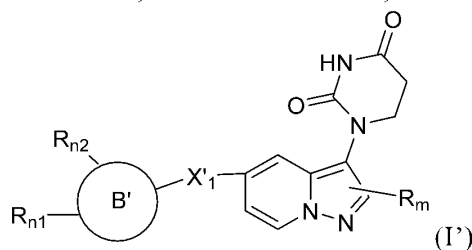
each R¹ is independently selected from the group consisting of H, deuterium, C₁-C₆ alkyl, and halogen;

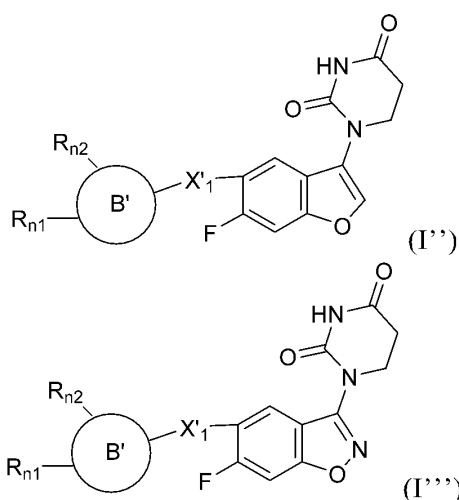
each R² is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C₁-C₆ alkyl, and C₁-C₆ haloalkyl;

each R³ and R⁵ is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₆ alkanoyl, C₂-C₆ alkylester, C₁-C₆ thioalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, hydroxy C₁-C₆ alkyl, C₃-C₇ cycloalkyl, and 3 to 8-membered heterocyclyl, wherein the cycloalkyl, and heterocyclyl are optionally substituted with halogen, CN and -OMe;

each R⁴ and R⁶ is independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, and -OH.

3. A compound of formula (I'), (I'') or (I'''), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,





wherein

- R_m is independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, and -OH;

X'1 is -(CH₂)_m-, -CH(R_{n3})(CH₂)_m-, -C(O)-, or -S(O)₂-;

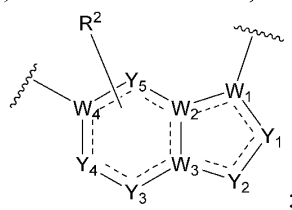
- Ring B' is independently selected from the group consisting of C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C₆-C₁₀ aryl, 5 to 10-membered heteroaryl, wherein the heterocyclyl, and heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N;

- R_{n1} and R_{n2} are each independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl, C₆-C₁₀ aryl, and 5 to 10-membered heteroaryl; wherein the alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 6 identical or different substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CN, -OH, C₃-C₈ cycloalkyl, 4 to 10 membered monocyclic or bicyclic heterocyclyl;

the H in -(CH₂)_m- can be optionally substituted with deuterium, C₁-C₆ alkyl, and halogen;

- m is 0, 1, 2, or 3.

4. The compound of claim 2, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein Ring A is 9-membered heteroaryl, and



preferably, Ring A is

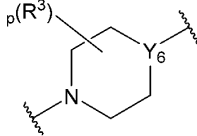
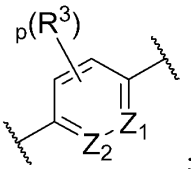
wherein ----- is a single bond or a double bond;

R^2 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl, and C_1 - C_6 haloalkyl;

Y_1 , Y_2 , Y_3 , Y_4 and Y_5 are each independently selected from the group consisting of C, CH, N, O, S and CO;

W_1 , W_2 , W_3 and W_4 are each independently selected from the group consisting of C, and N.

5. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein

10 Ring B is selected from the group consisting of  and  ;

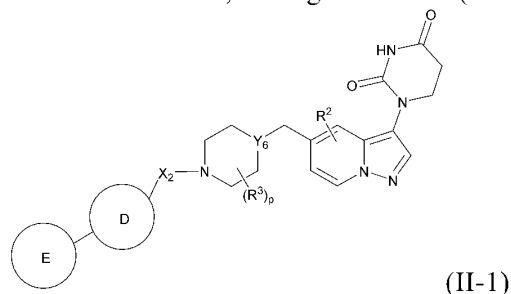
Y_6 is independently selected from the group consisting of CH and N;

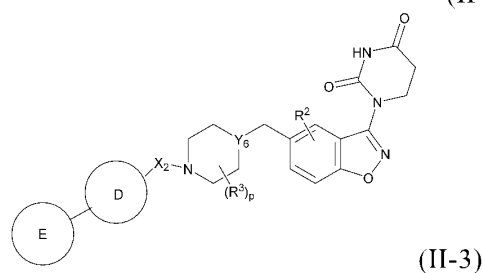
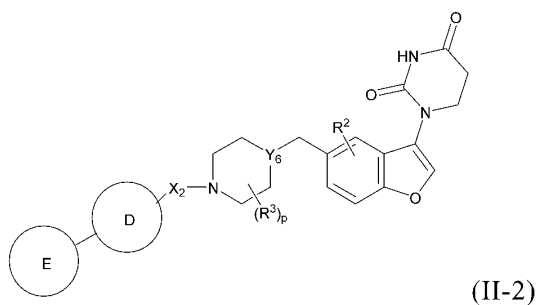
Z_1 and Z_2 are each independently selected from the group consisting of CH and N;

each R^3 is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyloxy, C_2 - C_6 alkynyloxy, C_2 - C_6 alkanoyl, C_2 - C_6 alkylester, C_1 - C_6 thioalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, hydroxy C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, and 3 to 8-membered heterocyclyl, wherein the cycloalkyl, and heterocyclyl are optionally substituted with halogen, CN and -OMe;

20 p is 0, 1, 2, 3 or 4.

6. The compound of claim 2, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, having a Formula (II-1)-(II-3),





wherein, each X_2 is independently selected from the group consisting of a bond, $-(CH_2)_n-$, $-\text{CH}(R^1)(CH_2)_n-$, $-\text{C}(\text{O})-$, and $-\text{S}(\text{O})_2-$;

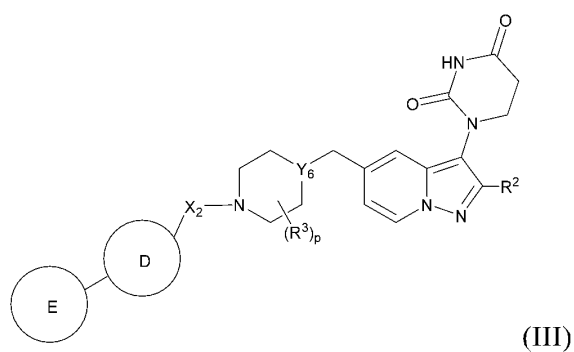
5 Y_6 is independently selected from the group consisting of CH and N;

p is 0, 1, 2, 3 or 4;

n is 0, 1, 2 or 3;

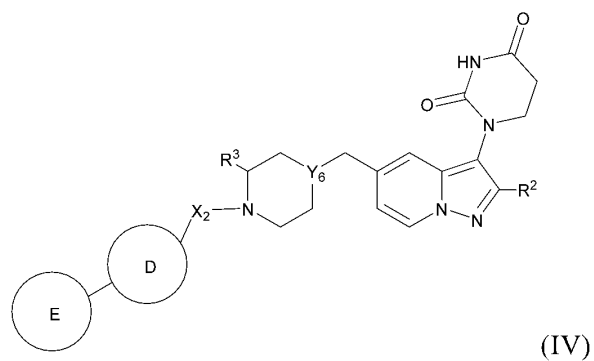
R^1 , R^2 , R^3 , Ring D and Ring E are defined as claim 2.

7. The compound of claim 6, or a pharmaceutically acceptable salt, hydrate, solvate,
10 prodrug, stereoisomer, or tautomer thereof, wherein the compound has a structure of formula (III)



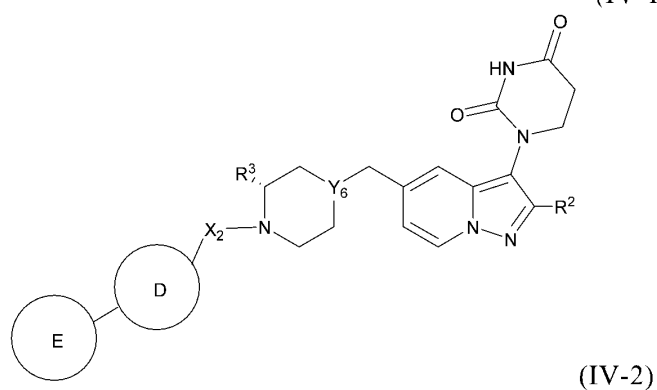
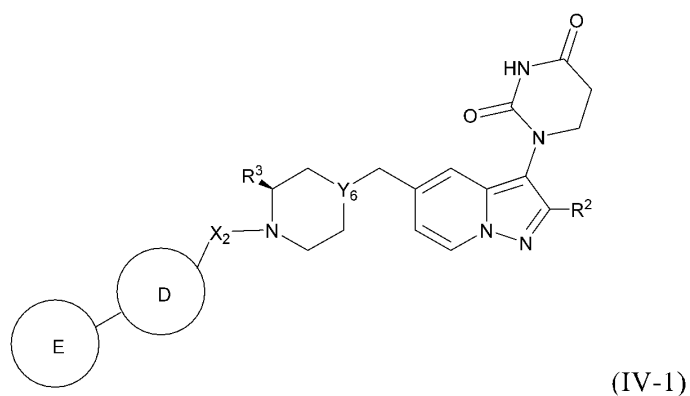
R^2 , R^3 , X_2 , p , Y_6 , Ring D and Ring E are as defined in claim 6.

15 8. The compound of claim 6, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the compound has a structure of formula (IV)



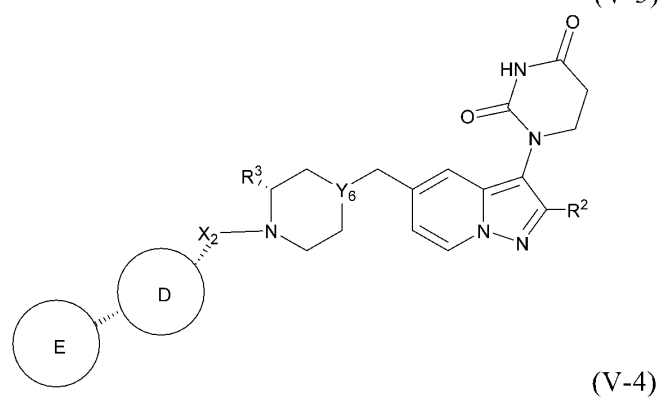
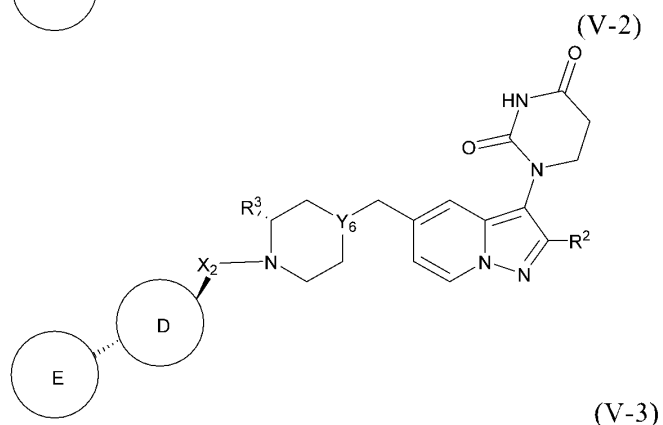
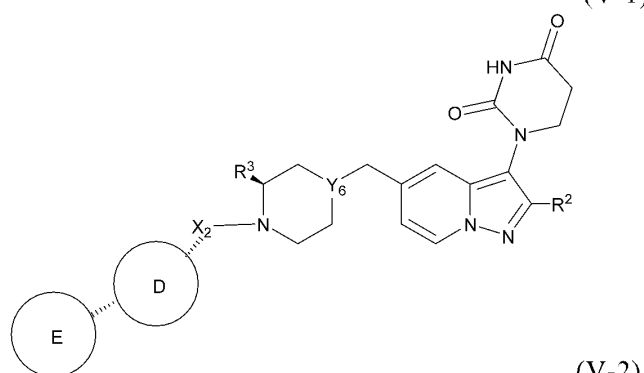
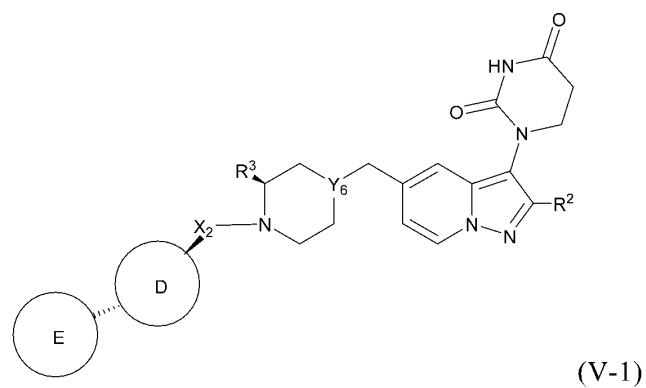
R^2 , R^3 , X_2 , Y_6 , Ring D and Ring E are as defined in claim 6.

9. The compound of claim 8, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the compound has a structure represented by a formula selected from the following formulas:



wherein R^2 , R^3 , X_2 , Y_6 , Ring D and Ring E are as defined in claim 8.

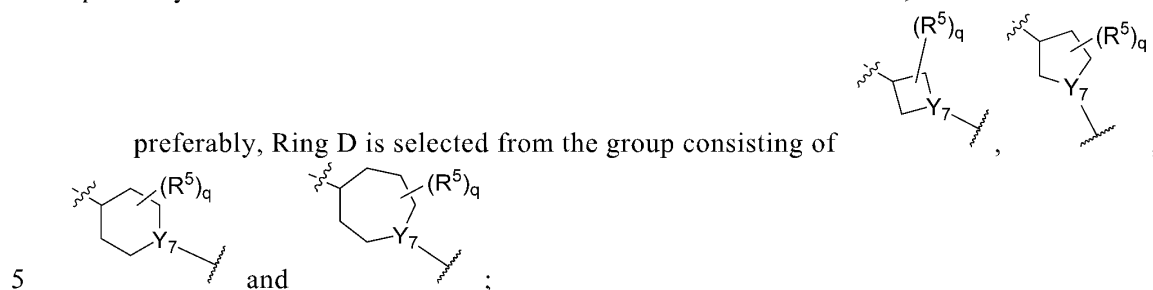
10. The compound of claim 8, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the compound has a structure represented by a formula selected from the following formulas:



5 R^2 , R^3 , X_2 , Y_6 , Ring D and Ring E are as defined in claim 8.

11. The compound of claim 2, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein Ring D is selected from the group

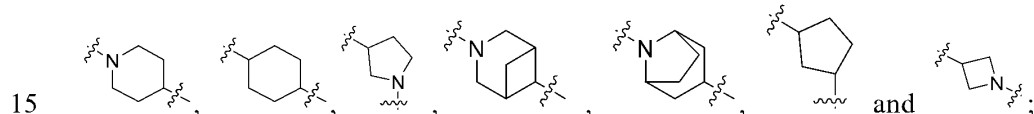
consisting of C₃-C₇ cycloalkyl (preferably, C₃-C₆ cycloalkyl), 4-8-membered heterocyclyl (preferably, 4-7-membered heterocyclyl), wherein the cycloalkyl and heterocyclyl are optionally substituted with 1 to 6 identical or different substituents R⁵;



wherein, each R⁵ is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₆ alkanoyl, C₂-C₆ alkylester, C₁-C₆ thioalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, hydroxy C₁-C₆ alkyl, C₃-C₇ cycloalkyl, and 3 to 8-membered heterocyclyl, wherein the cycloalkyl, and heterocyclyl are optionally substituted with halogen, CN and -OMe; or two R⁵ on non-adjacent carbon atoms together with the non-adjacent carbon atoms to which they are attached form a bridging ring;

Y₇ is independently selected from the group consisting of CH and N;

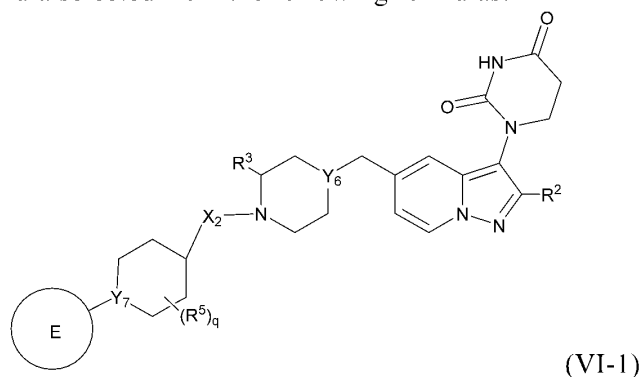
q is 0, 1, 2 or 3; more preferably, Ring D is selected from the group consisting of

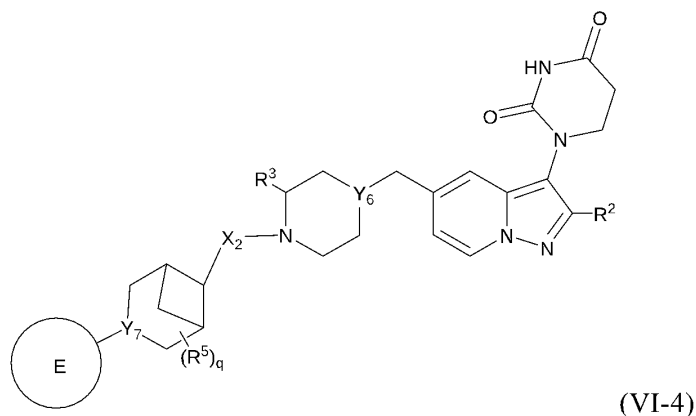
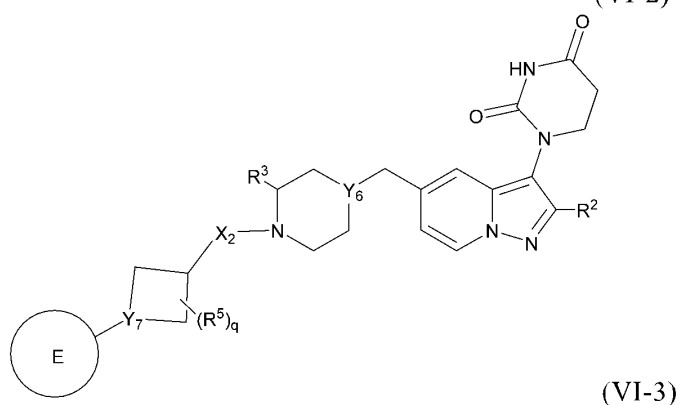
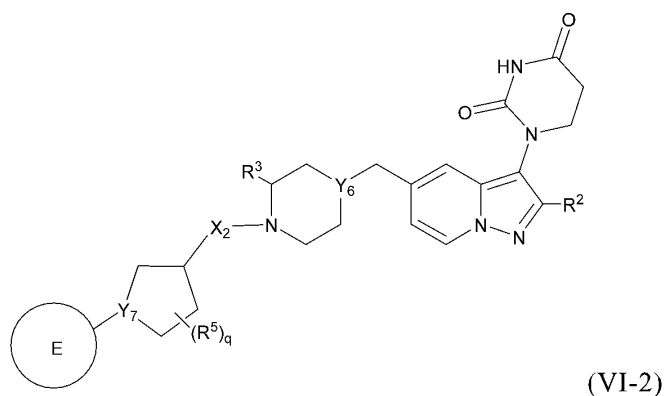


more preferably, each R⁵ is independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, C₁-C₃ alkyl, C₃-C₇ cycloalkyl, C₁-C₃ haloalkyl;

wherein when q is greater than or equal to 2, two R⁵ are optionally taken together with atoms to which they are bound to form a carbocyclyl or heterocyclyl ring.

12. The compound of claim 2, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the compound has a structure represented by a formula selected from the following formulas:



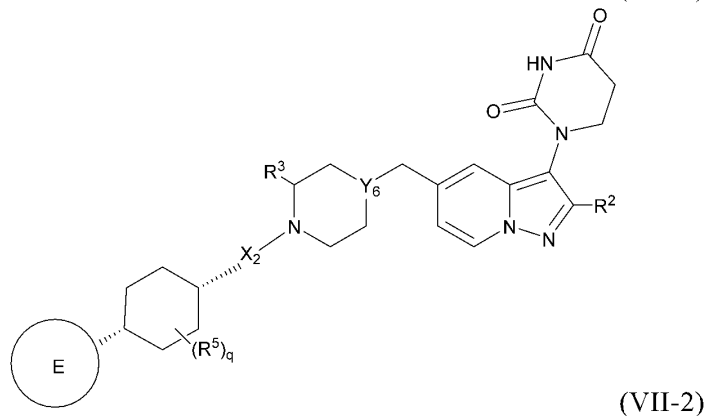
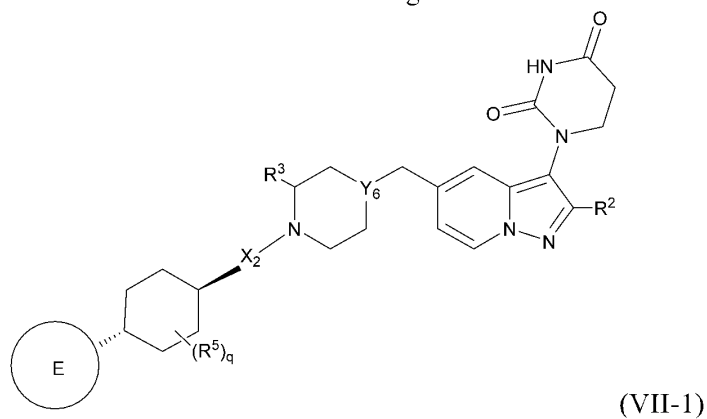


- 5 wherein Y_6 is independently selected from the group consisting of CH and N;
 Y_7 is independently selected from the group consisting of CH and N;
 each R^5 is independently selected from the group consisting of hydrogen, halogen,
 hydroxyl, nitro, cyano, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_2 - C_6
 alkenyloxy, C_2 - C_6 alkynyloxy, C_2 - C_6 alkanoyl, C_2 - C_6 alkylester, C_1 - C_6 thioalkyl, C_1 - C_6
 10 haloalkyl, C_1 - C_6 haloalkoxy, hydroxy C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, and 3 to 8-membered
 heterocyclyl, wherein the cycloalkyl, and heterocyclyl are optionally substituted with
 halogen, CN and -OMe; or two R^5 on non-adjacent carbon atoms together with the
 non-adjacent carbon atoms to which they are attached form a bridging ring;

q is 0, 1, 2 or 3

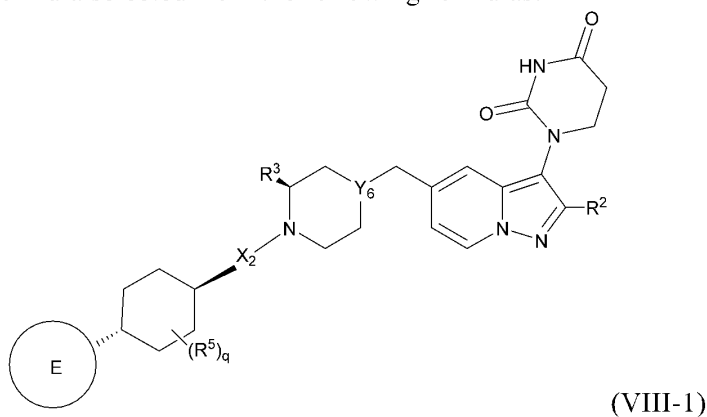
R^2 , R^3 , X_2 , and Ring E are as defined in claim 2.

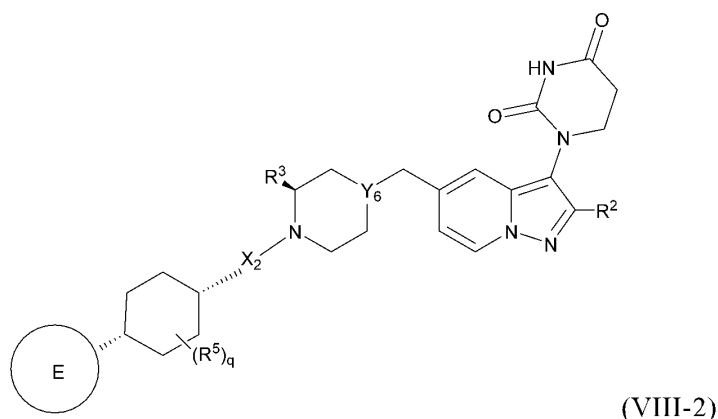
13. The compound of claim 12, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the compound has a structure represented by a formula selected from the following formulas:



wherein R^2 , R^3 , R^5 , X_2 , q, Y_6 , and Ring E are as defined in claim 12.

14. The compound of claim 13, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the compound has a structure represented by a formula selected from the following formulas:





wherein R^2 , R^3 , R^5 , X_2 , q , Y_6 , and Ring E are as defined in claim 13.

15. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein Ring E is a 5- to 9- membered heteroaryl, wherein the heteroaryl have 1, 2 or 3 heteroatoms as ring members which are each independently selected from the group consisting of O, S, and N; wherein the heteroaryl are optionally substituted with 1 to 3 identical or different substituents R^6 ;

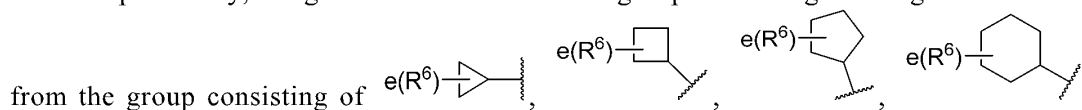
wherein each R^6 is independently selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-CN$, $-OH$, C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl.

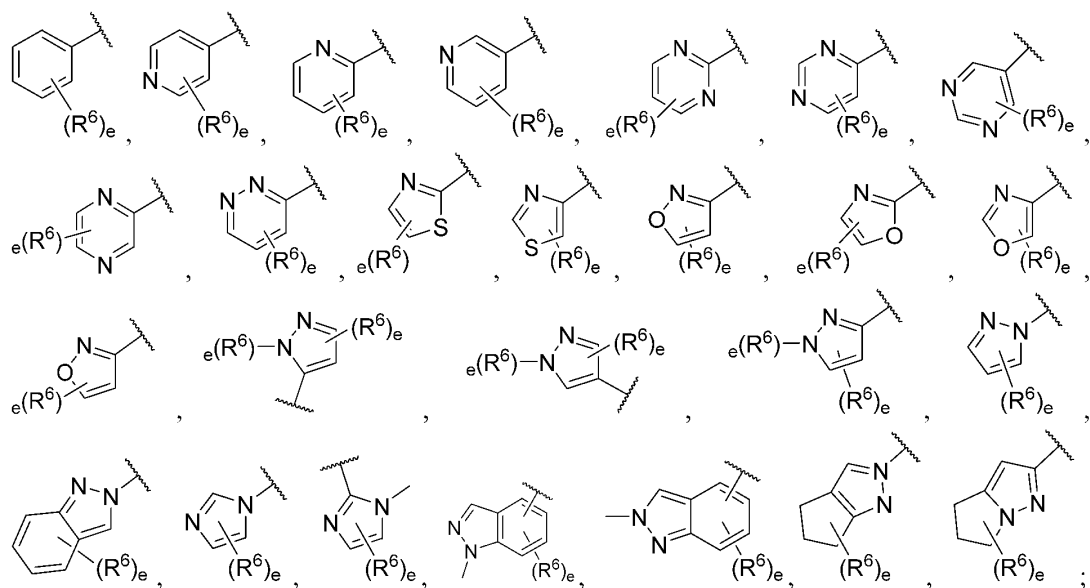
16. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein Ring E is selected from the group consisting of C_3 - C_6 cycloalkyl, 4-6 membered heterocyclyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl, pyrazolyl, indazolyl; wherein the cycloalkyl, heterocyclyl, thiazolyl, imidazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrazolyl, indazolyl are optionally substituted with 1 to 6 identical or different substituents R^6 ;

20 wherein, each R^6 is independently selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_2 - C_6 alkynyl, C_2 - C_6 alkynyloxy, $-CN$, $-OH$, C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl, C_5 - C_{10} heteroaryl;

e is 0, 1, 2, 3, 4, or 5;

25 more preferably, Ring E is selected from the group consisting of Ring E is selected

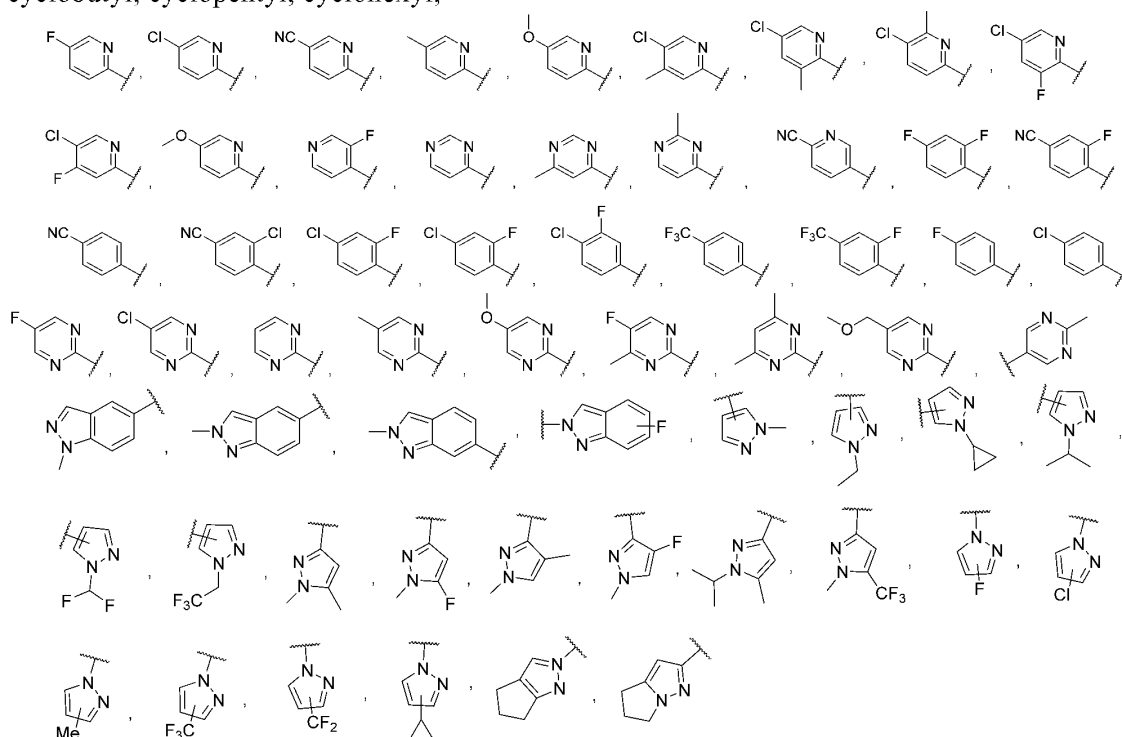




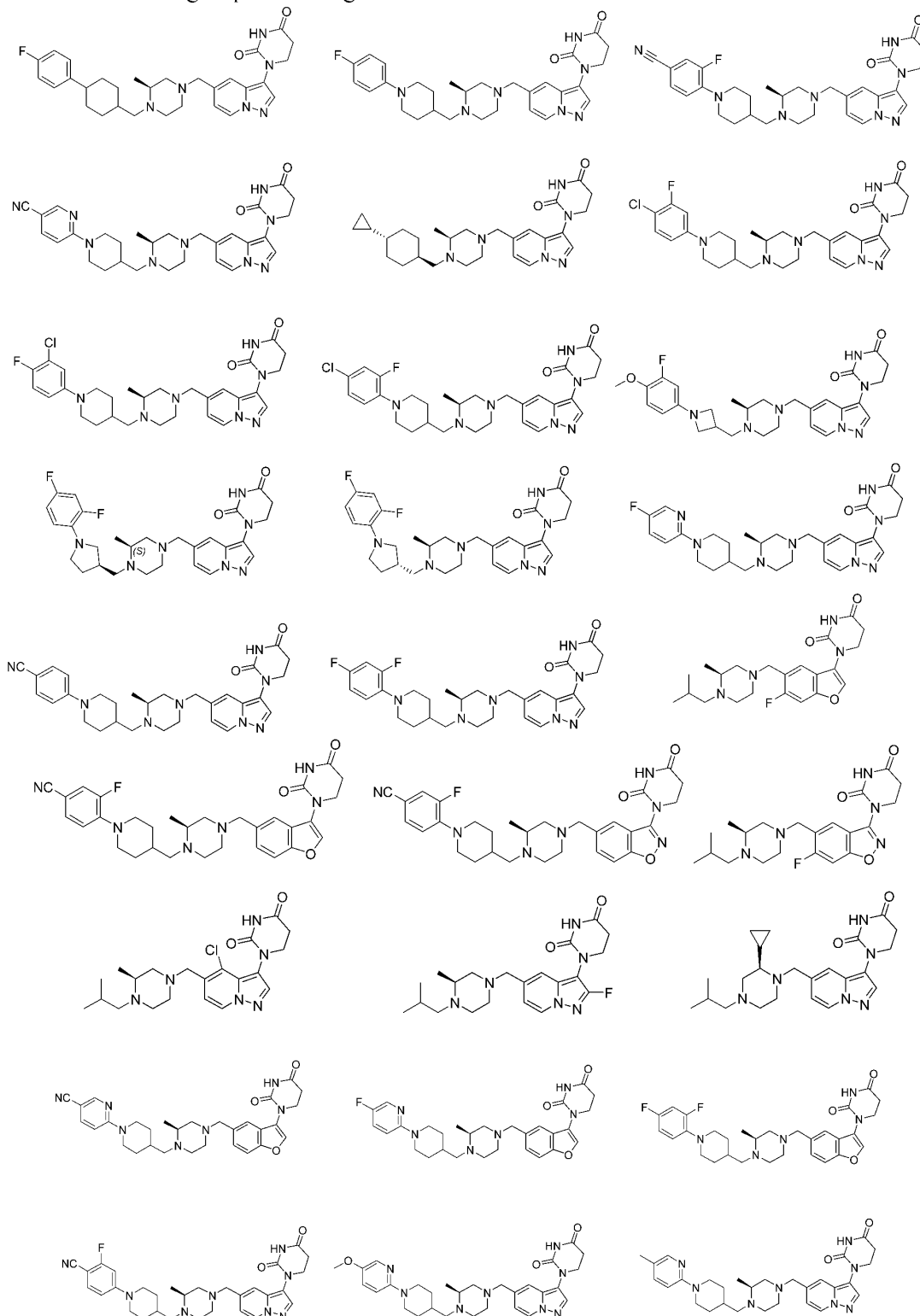
- 5 wherein, each R^6 is independently selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-CN$, $-OH$, C_3 - C_8 cycloalkyl, 3 to 8-membered heterocyclyl;

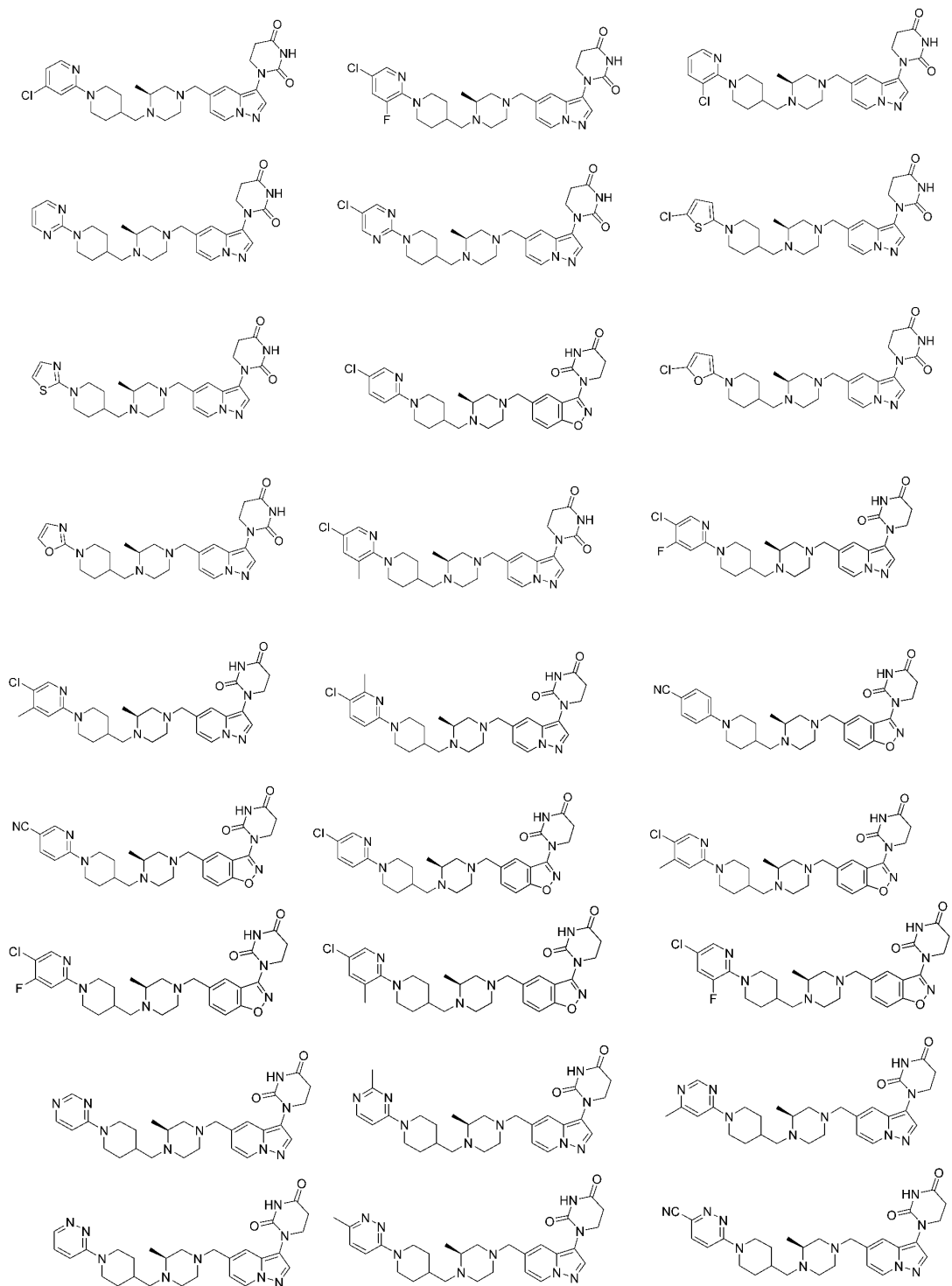
e is 0, 1, 2, 3, 4, or 5;

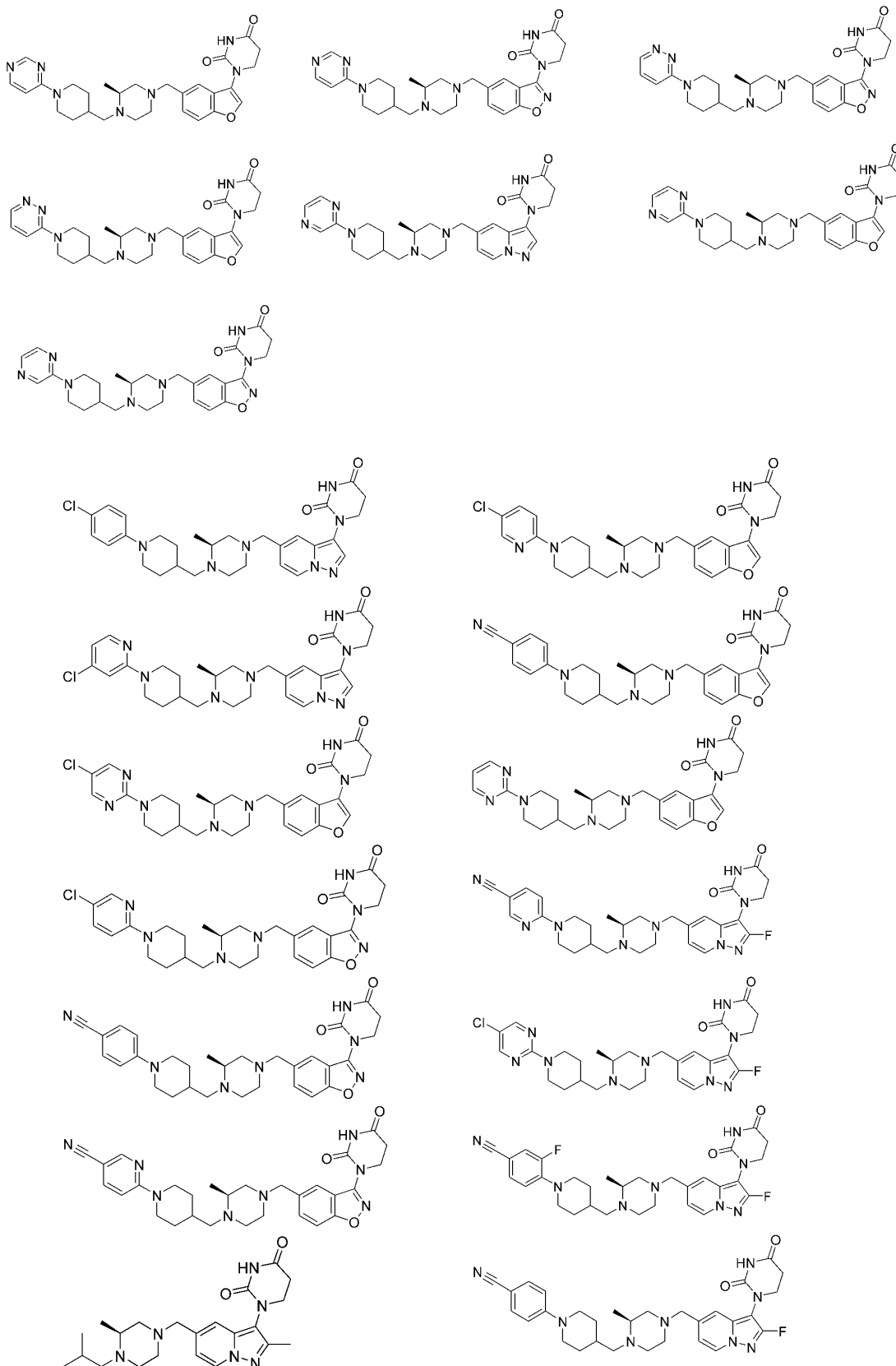
- more preferably, Ring E is selected from the group consisting of cyclopropyl,
 10 cyclobutyl, cyclopentyl, cyclohexyl,

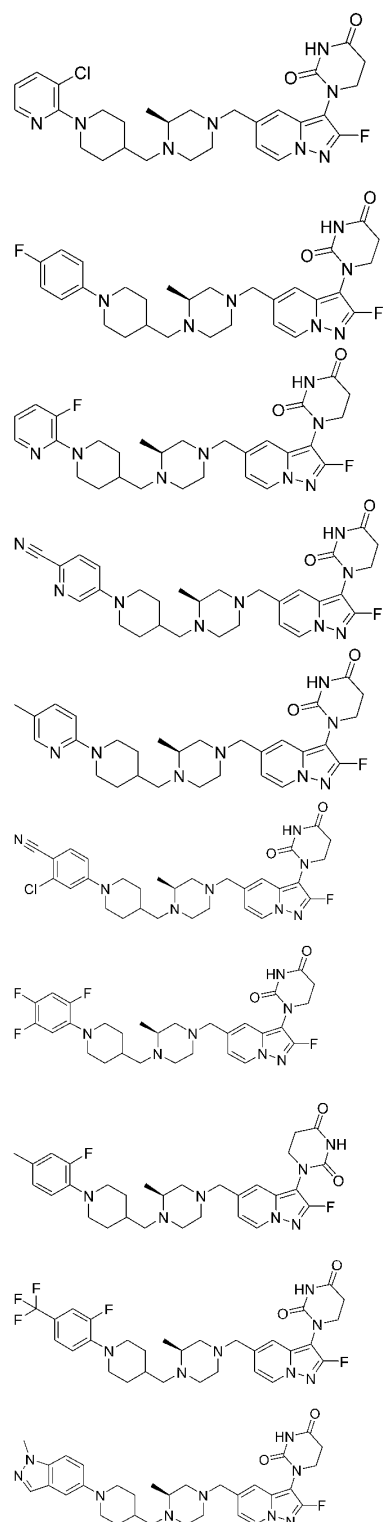
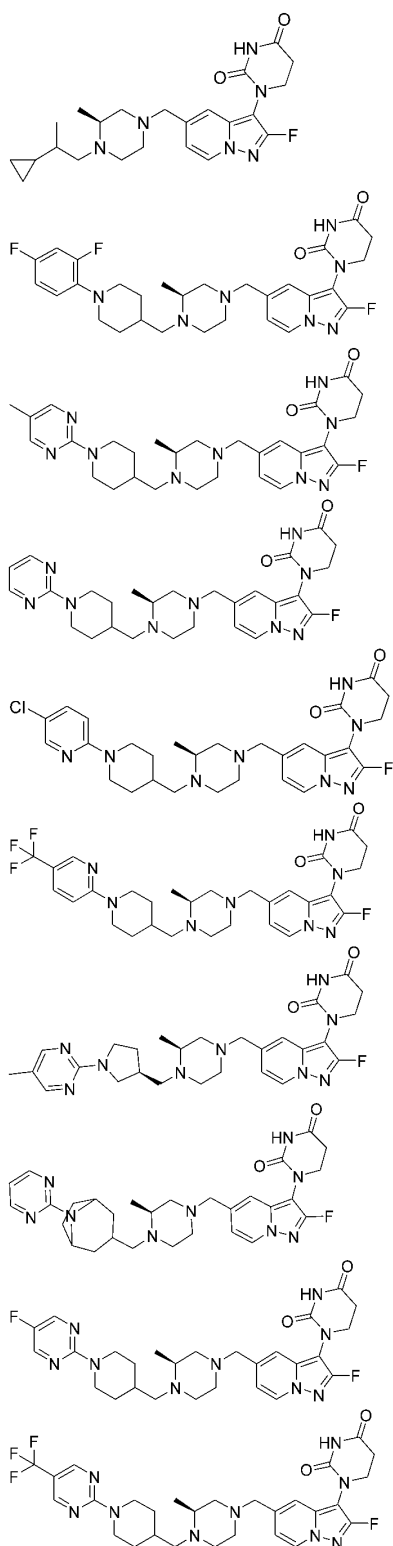


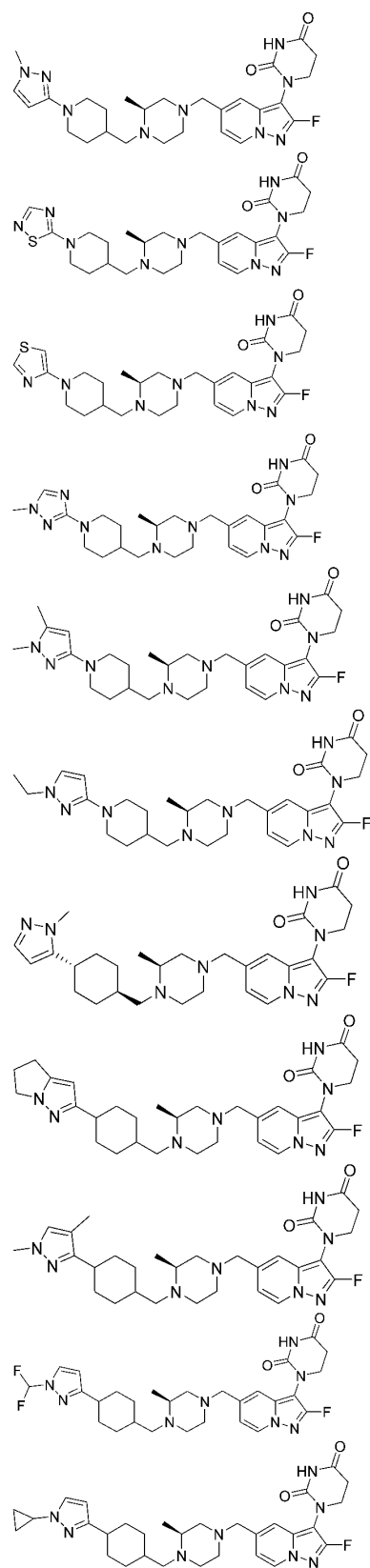
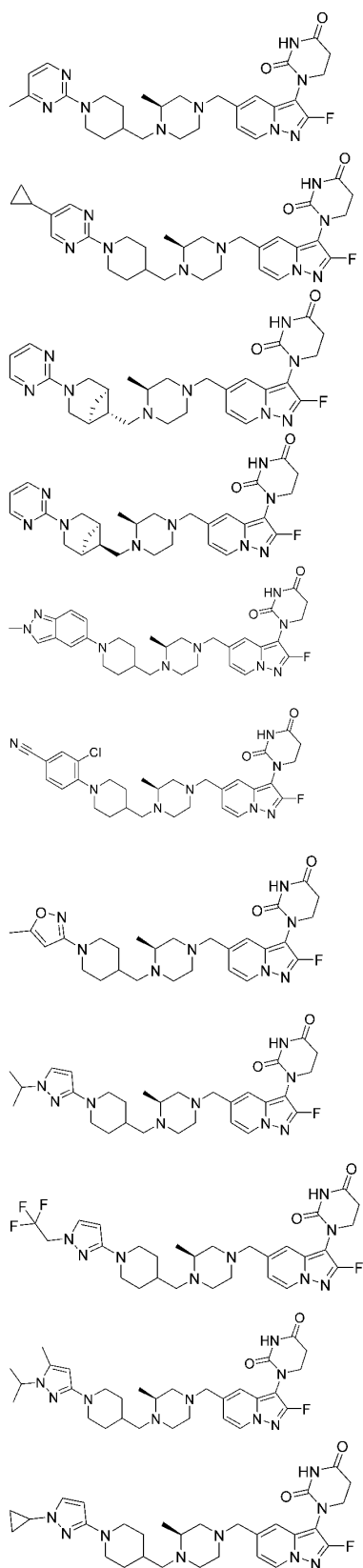
17. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, which is selected from the group consisting of:

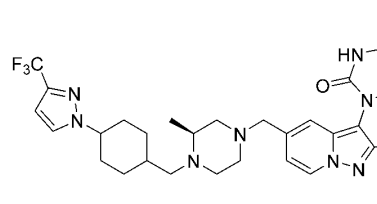
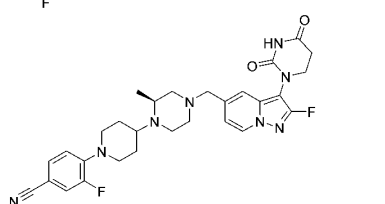
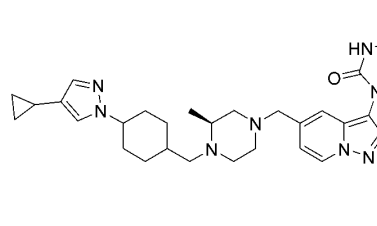
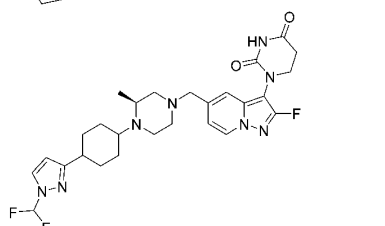
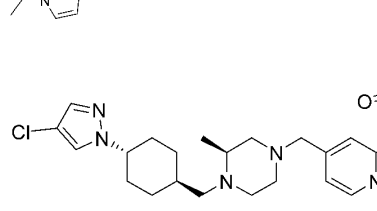
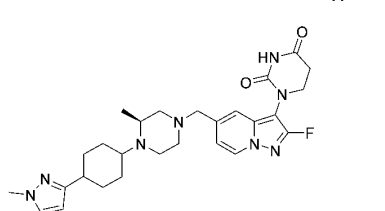
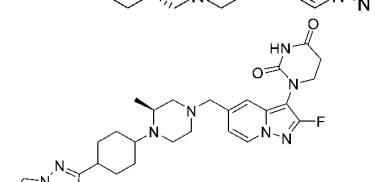
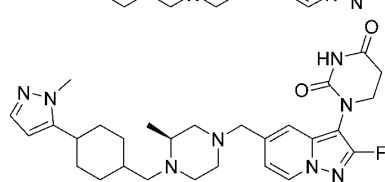
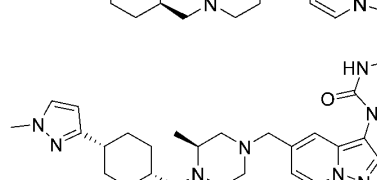
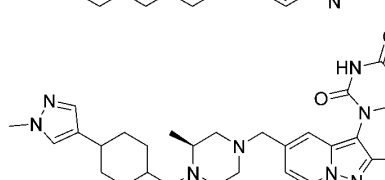
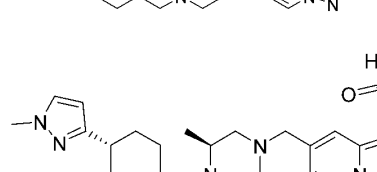
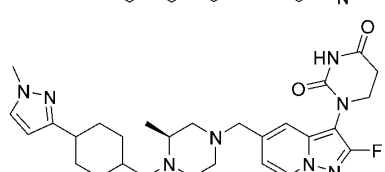
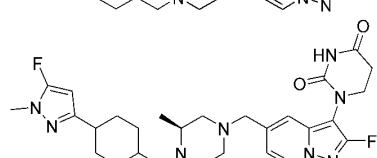
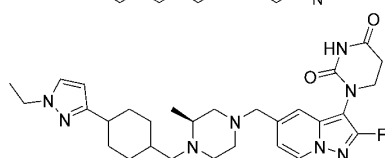
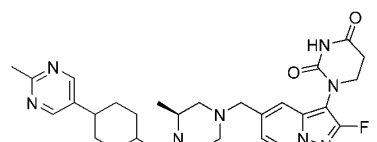
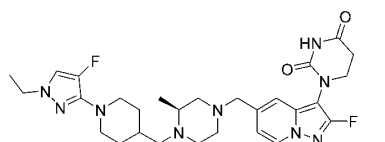
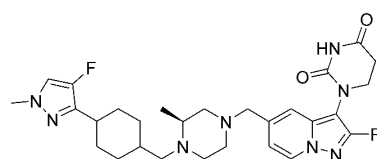
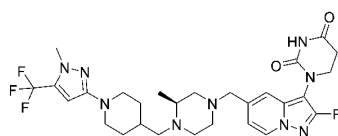


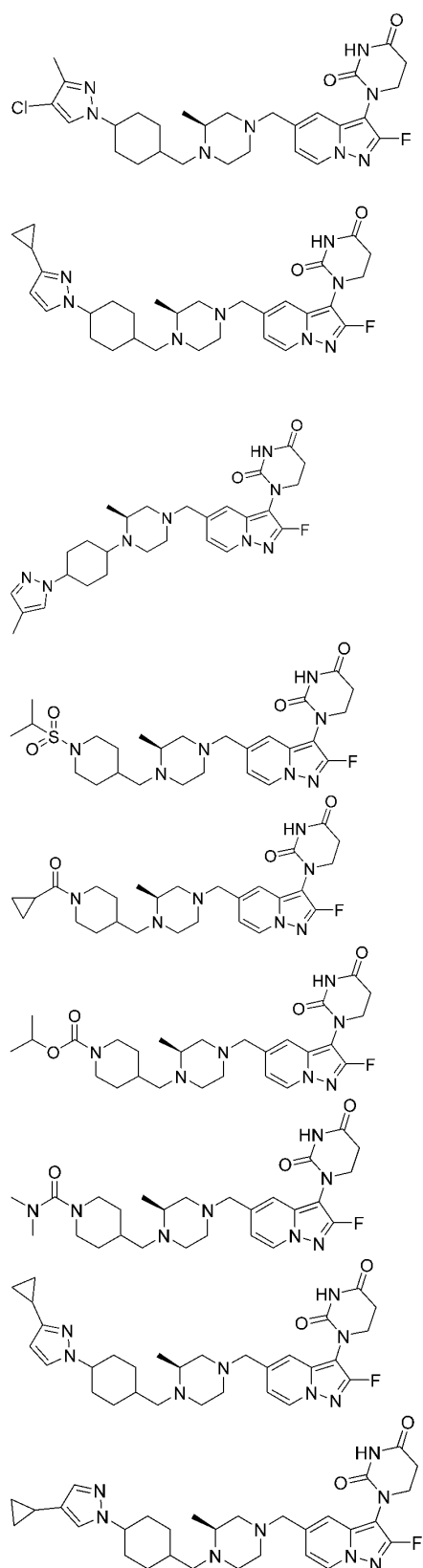
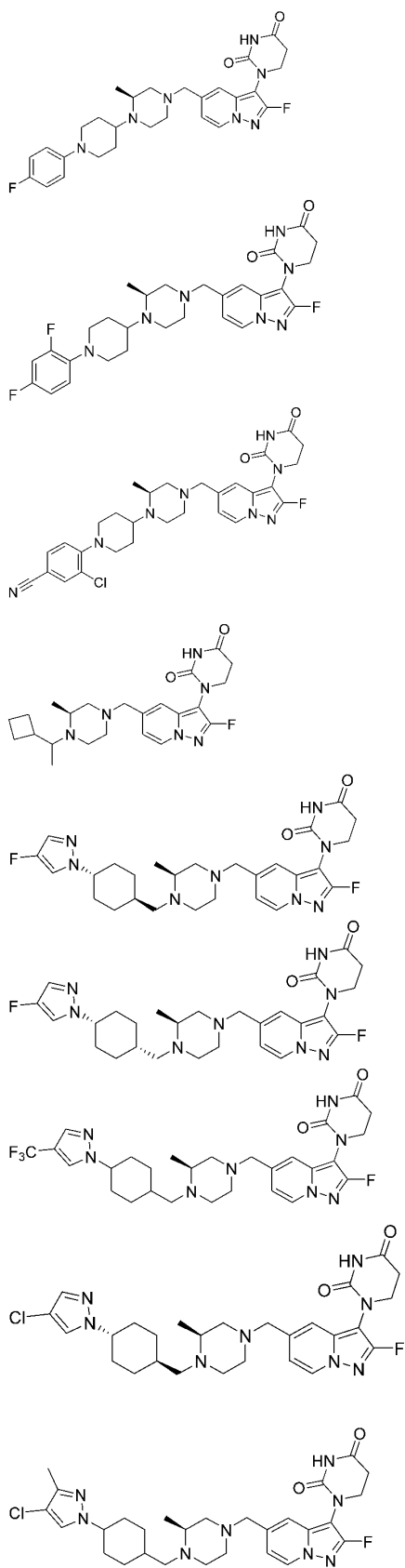


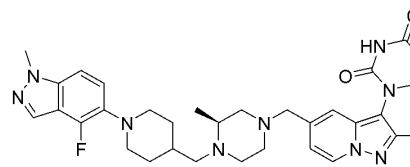
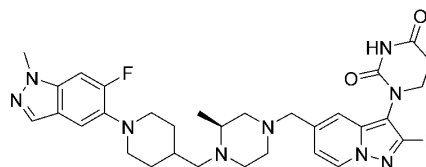
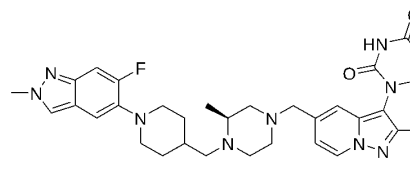
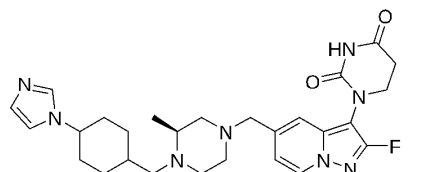
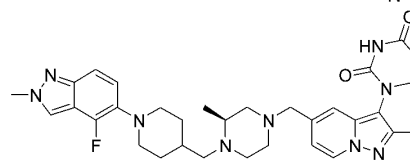
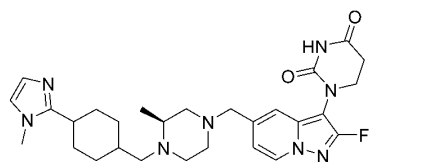
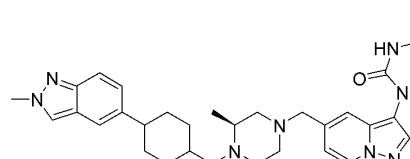
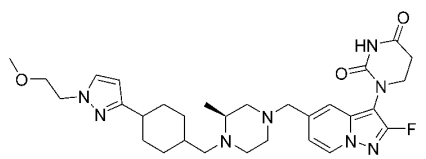
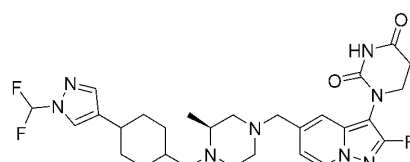
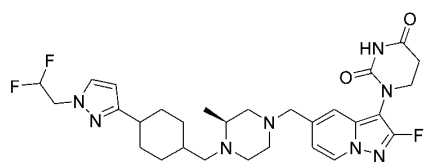
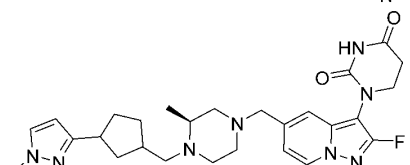
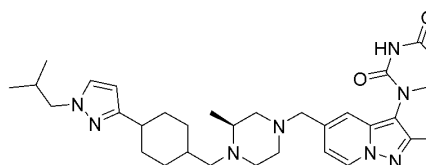
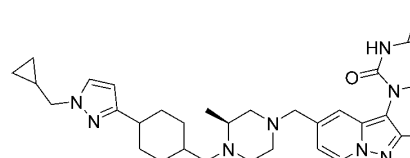
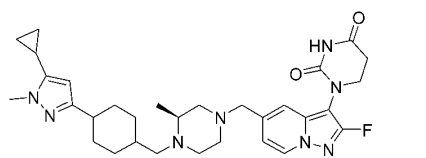
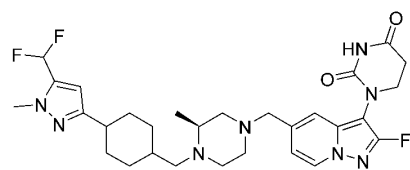
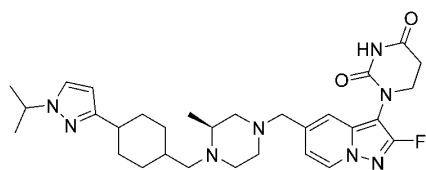


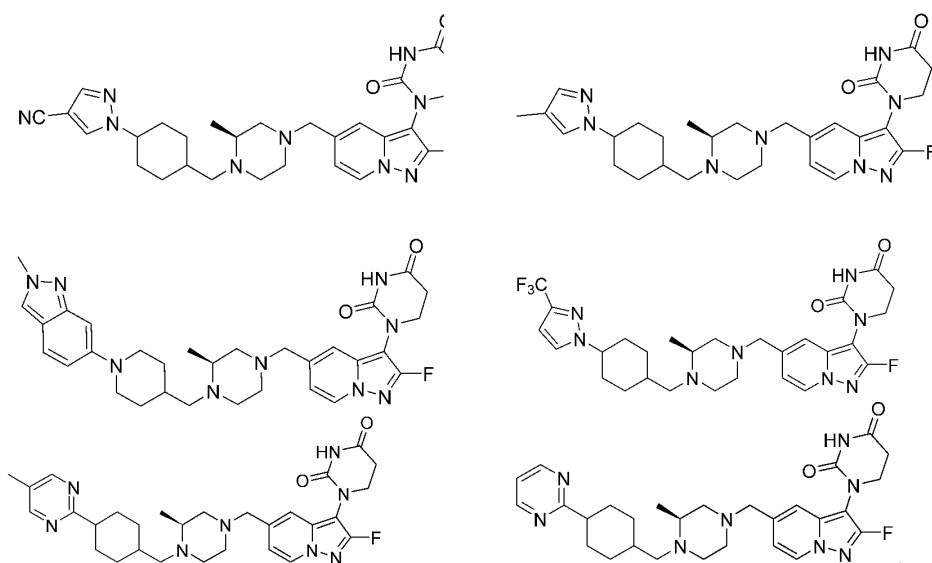




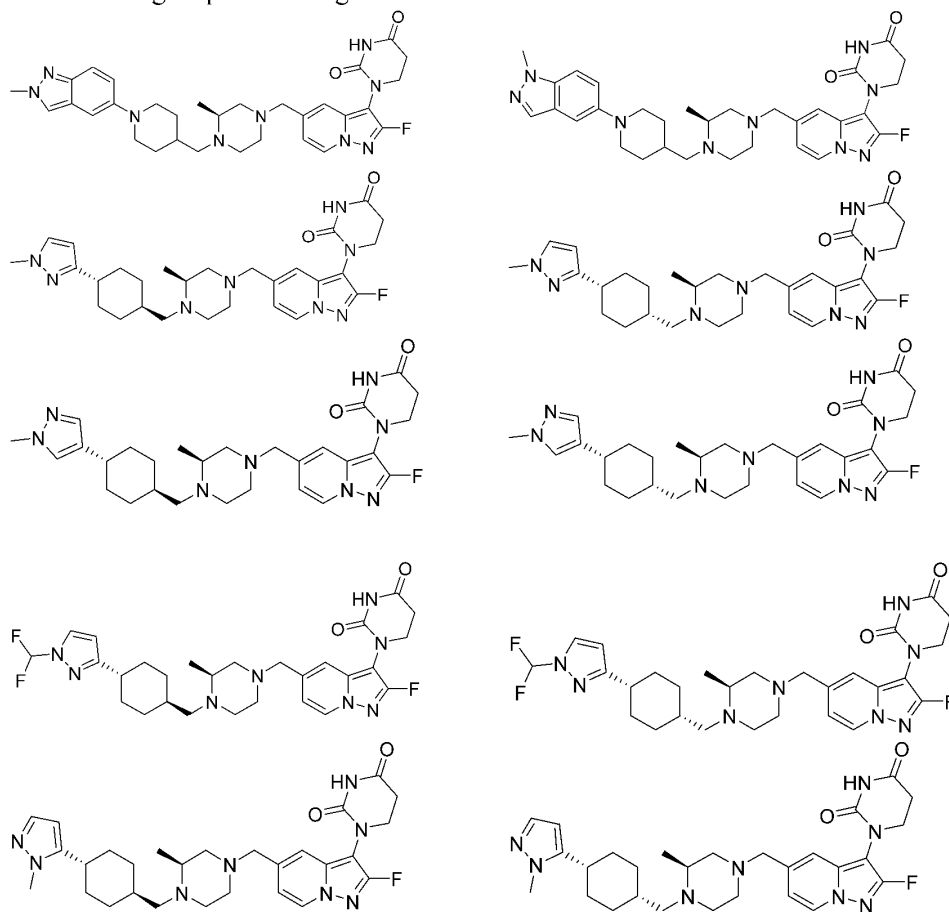


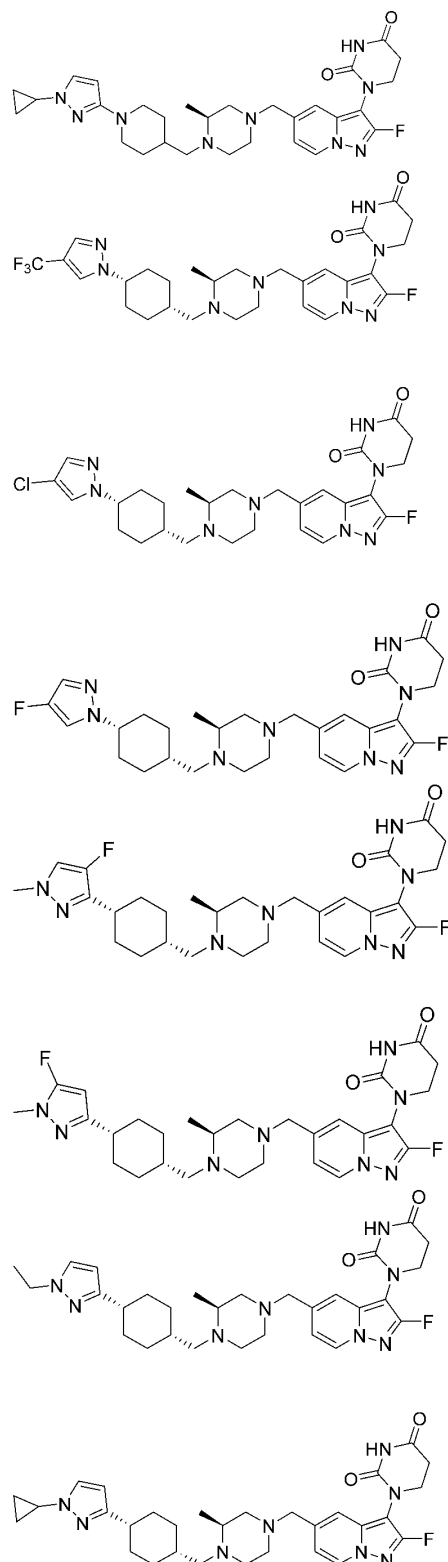
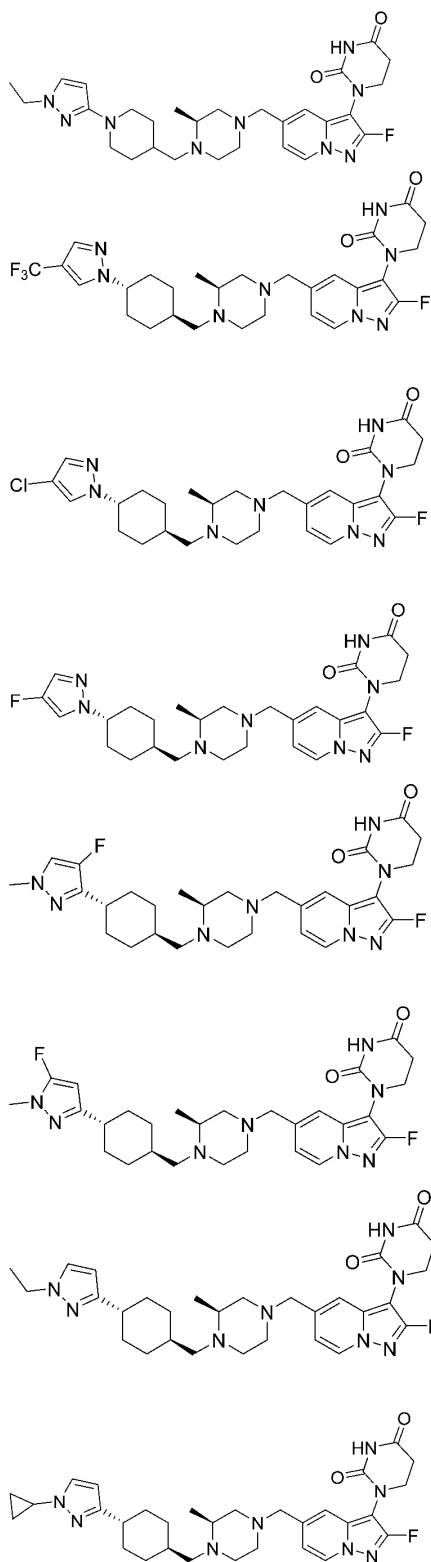


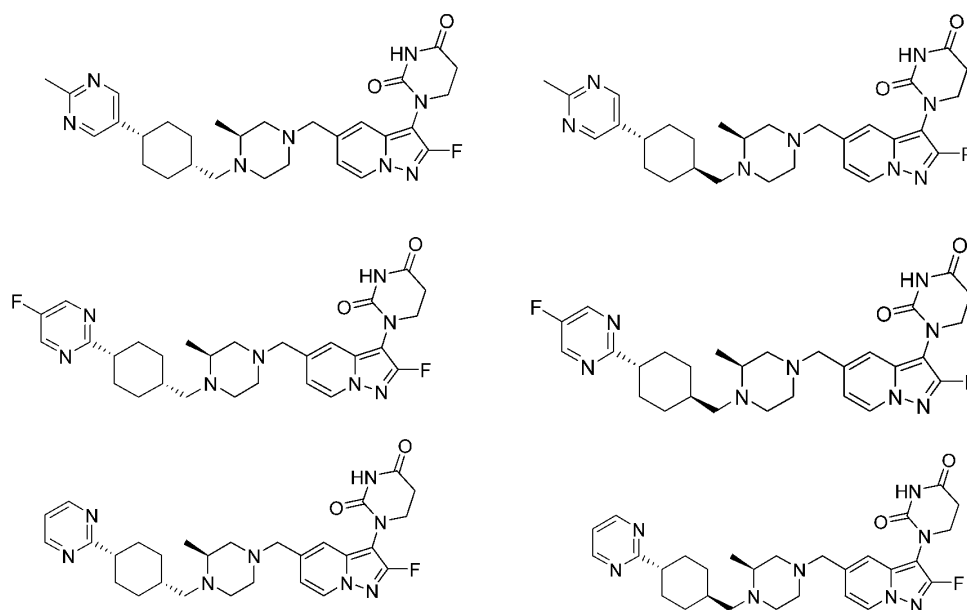




18. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, which is selected from the group consisting of:







19. A pharmaceutical composition comprising a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

20. Use of a compound of any one of claims 1-18 or a pharmaceutically acceptable salt,

5 hydrate, solvate, prodrug, stereoisomer, or tautomer thereof in the manufacture of a medicament for the treatment of a disease or disorder that is affected by the degradation of WIZ protein.

21. A method of treating a disease or disorder selected from sickle cell anemia, and beta-thalassemia in a subject in need thereof, comprising administering to a subject in need

10 thereof a therapeutically effective amount of the compound of any one of claims 1-18 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.