

# **FIVE-MEMBER-HETEROCYCLE FUSED PYRIDINE COMPOUNDS, METHOD OF PRODUCING THE SAME, AND USE THEREOF**

## **TECHNICAL FIELD**

This invention relates to a class of five-member-heterocycle fused pyridine  
5 compounds having inhibitory activity against protein tyrosine kinase, particularly c-Met,  
as well as pharmaceutically acceptable salts or pharmaceutically acceptable solvates of  
said compounds, process for producing the same, pharmaceutical compositions containing  
said compounds, and use of said compounds as inhibitors against protein tyrosine kinase,  
particularly as inhibitors against c-Met, as well as use of the same in preparation of  
10 medicament for preventing and/or treating protein diseases and tumors associated with  
abnormal protein tyrosine kinase.

## **BACKGROUND ART**

Based on data published by Ministry of Health on major causes for death among  
Chinese urban and rural residents during 2007-2012, the top three causes for death among  
15 urban residents are malignant cancer, cerebrovascular disease and heart disease, while the  
top three causes for death among rural residents are malignant tumors, cerebrovascular  
disease and respiratory diseases, wherein mortality due to malignant cancer is steadily  
rising. Accordingly, malignant cancer has become the leading cause for death of Chinese  
residents, and its development is accelerating.

20 In recent years, along with deepening life science research and the rapid progress,  
receptor tyrosine kinases, which exhibit aberrant activation in cancer, has become an  
important target in the anticancer drug research and development because of the critical  
roles they play in tumorigenesis, invasion and metastasis, drug resistance, etc.

Protein tyrosine kinases (PTKs) are closely related to tumor development and  
25 progression. Protein tyrosine kinase hyperactivity may cause activation of downstream  
signaling pathways, in turn, lead to cell differentiation, proliferation, migration, and  
inhibition of apoptosis, and eventually, result in tumor formation and metastasis [Top  
Med Chem, 2007 (1): 83- 132]. Accordingly, protein tyrosine kinase inhibitor has become  
one of the fastest growing class of anticancer drugs, having a number of small molecule

protein tyrosine kinase inhibitors including lapatinib, sunitinib, crizotinib and the like marketed by the end of 2012. Compared with conventional cytotoxic anticancer drugs, these drugs exhibit improved selectivity, higher efficacy, less side effects, and have become the hotspot in anticancer drug research.

5       Hepatocyte Growth Factor (HGF) receptor c-Met is an important member of the receptor tyrosine kinase family. HGF is overexpressed and abnormally activated in most cancers and some sarcomas, closely associated with poor prognosis in patients having cancer, such as lung cancer, stomach cancer, liver cancer, breast cancer, colon cancer, prostate cancer, pancreatic cancer, esophageal cancer, ovarian cancer, kidney cancer,  
10       glioma, thyroid cancer, melanoma, etc. Upon activation through interaction with HGF or otherwise, c-Met induces tumor cell proliferation and resistance to apoptosis, promote tumor cell migration, invasion, and angiogenesis (*Nature Reviews Drug Discovery* 2008, 7, 504-516; *Nat Rev Cancer*. 2012; 12 (2): 89-103). Unlike other kinases, c-Met, a critical node in tumor signaling pathways, may interact with other tumor-associated molecules on  
15       cell surface to activate and magnify tumor-related effects through crosslinking, and promote tumor development and metastasis (*Nature Reviews Drug Discovery* 2008, 7, 504-516.). In addition, abnormal activation of HGF/c-Met is closely associated with resistance to inhibitors against EGFR, HER2, and B-Raf as well as some  
20       chemotherapeutic drugs (*Science* 2007, 316, 1039-1043; *Clinical Cancer Research* 2011, 17, 2260-2269; *Nature* 2012 Jul 26; 487(7408): 500-4; *British Journal of Cancer* 2012, 107, 793-799). Accordingly, investigation targeting c-Met inhibitors has become one hot frontier in anticancer drug researches.

Therefore, there is an pressing need for development of novel protein tyrosine kinase inhibitor having new structure, high activity, and low toxic side effects. As a  
25       receptor-type protein tyrosine kinase, c-Met is expressed in both normal cells and tumor cells. Normal HGF/c-Met signal transduction plays an important role in embryonic development, tissue repair, whereas abnormal HGF/c-Met signal transduction is closely associated with tumorigenesis, especially, with invasion and metastasis (Gao GF, Vande Woude GF. HGF/SR-Met signaling in tumor progression, *Cell Res*, 2005, 15(1): 49-51).  
30       Overexpression of c-Met is found in human hepatocellular carcinoma,

cholangiocarcinoma, pancreatic cancer, lung cancer, thyroid cancer, pleural mesothelioma, etc., especially in metastatic tumors. Its role may include impacting adhesion of tumor cells, promoting degradation of extracellular matrix, inducing angiogenesis and promoting cell proliferation. All these indicate that c-Met is an important target for cancer therapeutics. Currently, blocking HGF/c-Met signal transduction is an important strategy for antitumor therapy. Since c-Met inhibitors, especially small molecule inhibitors as anticancer drugs are mostly in clinical studies and yet to be marketed, and antibody drugs are often more expensive, a broad space is available for development of these inhibitors. Accordingly, c-Met kinase is a promising target for anticancer drug researches. Although many inhibitors are developed against this signaling pathway, their structures are rather confined. This application designs a new class of 5-member-heterocycle fused pyridine compounds and discover that they possess desirable c-Met inhibitory activity.

### **SUMMARY OF THE INVENTION**

One object of this application is to provide a class of 5-member-heterocycle fused pyridine compounds, or pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof. Having structures shown in the formulae below, said compounds are protein tyrosine kinase inhibitors, particularly effective in inhibiting c-Met.

Another object of this application is to provide a process for producing compounds having structures shown in the formulae below, or pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof.

Still another object of this application is to provide a use of compounds having structures shown in the formulae below, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, in preparation of medicaments serving as protein tyrosine inhibitors, particularly, c-Met inhibitors.

Yet another object of this application is to provide a use of compounds having structures shown in the formulae below, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, in preparation of medicaments for preventing or treating diseases associated with abnormal cell proliferation, morphological change and hyperkinesis related to abnormal protein tyrosine kinase in vivo, or diseases associated with angiogenesis or cancer metastasis, particularly, in preparation of

medicaments for treating or preventing tumor growth and metastasis.

Yet another object of this application is to provide a pharmaceutical composition comprising a compound having structures shown in formula I, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, as the active ingredient, said pharmaceutical composition may further comprise a pharmaceutically acceptable carrier.

Yet another object of this application is to provide a use of above pharmaceutical composition in preparation of medicaments for preventing or treating diseases associated with abnormal cell proliferation, morphological change and hyperkinesis related to abnormal protein tyrosine kinase in vivo, or diseases associated with angiogenesis or cancer metastasis, particularly, in preparation of medicaments for treating or preventing tumor growth and metastasis.

Yet another object of this application is to provide a method of preventing or treating diseases associated with abnormal cell proliferation, morphological change and hyperkinesis related to abnormal protein tyrosine kinase in vivo, and diseases related to angiogenesis or cancer metastasis, in a subject in need thereof. Said method comprises administering therapeutic effective amount of a compound having a structure shown in the formulae below, a pharmaceutically acceptable salt or pharmaceutically acceptable solvate of the same, or a pharmaceutical composition comprising a compound having a structure shown in the formulae below, a pharmaceutically acceptable salt or pharmaceutically acceptable solvate of the same, or a mixture thereof, as the active ingredient.

### **BRIEF DESCRIPTION OF THE DRAWING**

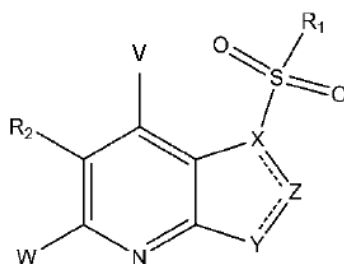
Fig. 1 shows the effect of the compound according to this invention on growth of human lung cancer EBC-1 xenograft in nude mice.

Fig. 2 shows the effect of the compound according to this invention on growth of human malignant glioblastoma cell U87MG xenograft in nude mice.

### **DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS**

In first aspect, this application provides a 5-member-heterocycle fused pyridine compound having structure shown below in Formula (X), a pharmaceutically acceptable

salt or pharmaceutically acceptable solvate of the same,



(X)

wherein,

5 X, Y and Z are each independently N or C, and at least one of X, Y and Z is N, provided that Z is N when X is N;

W and V are each independently selected from H, halogen, unsubstituted or halogen substituted C<sub>1</sub>-C<sub>4</sub> alkyl, unsubstituted or halogen substituted C<sub>1</sub>-C<sub>4</sub> alkoxy, nitro, or cyano;

10 R<sub>1</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5 to 10-membered heteroaryl comprising 1 to 5 heteroatom(s) selected from N, O, and S; or substituted or unsubstituted 4 to 10-membered heterocyclyl comprising 1 to 5 heteroatom(s) selected from N, O, and S; wherein substituent(s) in the substituted group(s) is halogen, nitro, cyano, hydroxyl, unsubstituted or halogen- or morpholinyl-substituted  
15 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), -OC(O)-R<sub>f</sub>, unsubstituted phenyl or phenyl substituted by 1 to 4 of R<sub>3</sub>, or unsubstituted 4- to 7-membered heteroaryl comprising 1 to 5 heteroatom(s) selected from N, O, and S or 4- to 7-membered heteroaryl comprising 1 to 5 heteroatom(s) selected from N, O, and S substituted by 1 to 4 of R<sub>4</sub>;

20 R<sub>2</sub> is cyano; C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl; -NR<sub>c</sub>R<sub>d</sub>; -NHC(O)-R<sub>e</sub>; substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl comprising 1 to 5 heteroatom(s) selected from N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl comprising 1 to 5 heteroatom(s) selected from N, O, and S; wherein substituent(s) in the substituted group(s) is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub>  
25 alkylendioxy, unsubstituted or halogen- or -NR<sub>c</sub>R<sub>d</sub>-substituted C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, morpholinyl

methyl, or unsubstituted or R''-substituted piperidinyl;

wherein R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylendioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl-substituted piperidinyl;

R' is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heterocyclyl;

R'' is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl, or unsubstituted or substituted benzoyl where substituent is selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>a</sub> and R<sub>b</sub> are each independently H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl;

R<sub>c</sub> and R<sub>d</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; alternatively, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl;

R<sub>e</sub> is unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkyl- or halogen- or C<sub>1</sub>-C<sub>6</sub> alkoxy-substituted C<sub>6</sub>-C<sub>20</sub> aryl, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heteroaryl.

For the purpose of this invention, the term "alkyl" used herein refers to unsubstituted or substituted, saturated hydrocarbon group containing from 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably 1 to 4 carbon atoms, unless otherwise stated. Preferably, alkyl includes, but not limited to, substituted or unsubstituted methyl, ethyl, propyl, isopropyl and butyl. The term "aryl" used herein refers to aromatic carbon cyclic group. Preferably, aryl includes, but not limited to, phenyl, tolyl, xylyl, cumenyl, naphthyl, biphenyl and fluorenyl. These groups can be substituted or unsubstituted. The term "heteroaryl" used herein refers to aromatic heterocyclyl, which may be a monocyclic or bicyclic group. Preferably, heteroaryl includes, but not limited to, thienyl, furanyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, tetrazolyl, benzothiazolyl, benzofuranyl, indole indolyl, isoindolyl, and the likes. The term "heterocyclyl" refers to saturated or unsaturated cyclic

group containing carbon atom(s) and 1 to 5 heteroatom(s). Preferably, heterocyclyl in this invention includes, but not limited to, piperaziny, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperidinyl. The term "halogen" refers to F, Cl, Br, or I. Preferably, the halogen is F, Cl and Br, and more preferably, Cl and F. The term "substituted" means replacing one or more, such as 2 or 3, hydrogen atoms of a group with substituent(s), for instance, single substitution, double substitution, or triple substitution. A person skilled in the art will appreciate that, when this term is used herein, it means any specific means of substitutions are explicitly and specifically disclosed, unless otherwise stated. --- represents single bond or double bond, and X, Y and Z abide by valence-bond theory. In this specification, substituents expressed with the same notation share the same definition, unless otherwise stated.

In one embodiment of this invention, W and V are each independently selected from H, halogen, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl. More preferably, W is H, V is independently selected from H, halogen, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl.

In any of the above embodiments, X and Z are N, Y is C. In another preferred embodiment, X and Z are C, Y is N. In another preferred embodiment, X is C, Y and Z are N.

In any of the above embodiments, R<sub>1</sub> is preferably substituted or unsubstituted C<sub>6</sub>-C<sub>10</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl comprising 1 to 5 heteroatom(s) selected from N, O, and S; or substituted or unsubstituted 5- to 10-membered heterocyclyl comprising 1 to 5 heteroatom(s) selected from N, O, and S. More preferably, R<sub>1</sub> is selected from substituted or unsubstituted phenyl, naphthyl, isoxazolyl, 8- to 10-membered bicyclic heteroaryl comprising 2 to 3 heteroatoms selected from N, O, and S (such as imidazo[2,1-b]thiazolyl, imidazo[1,2-a]pyridinyl, benzo[1,2,5]oxadiazolyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]imidazolyl, imidazo[1,2-a]pyrimidinyl, and the likes). Substituent(s) in R<sub>1</sub> is halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>5</sub> alkyl, hydroxyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, C<sub>1</sub>-C<sub>5</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), -OC(O)-R<sub>f</sub>, unsubstituted phenyl or phenyl substituted by 1 to 3 of R<sub>3</sub>, or unsubstituted 5- to

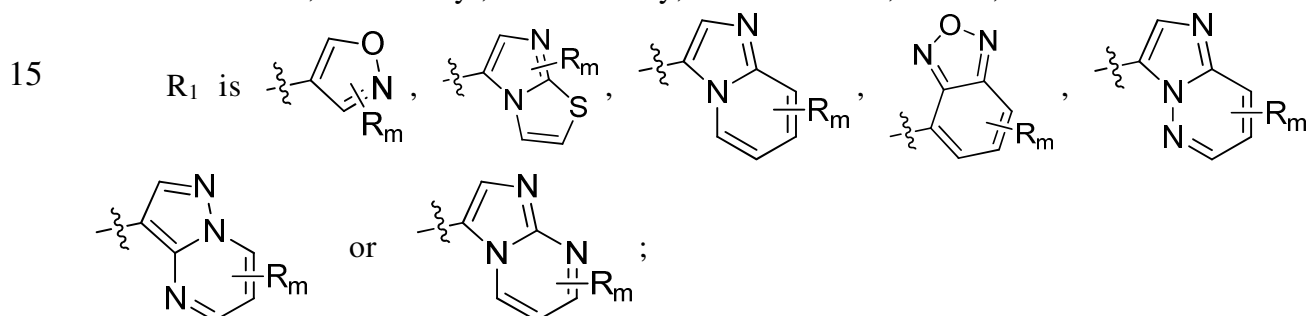
7-membered heteroaryl comprising 1-3 heteroatom(s) selected from N, O, and S or 5- to 7-membered heteroaryl comprising 1-3 heteroatom(s) selected from N, O, and S substituted by 1 to 3 of R<sub>4</sub>; wherein the heteroaryl is preferably furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranyl, pyridinyl, morpholinyl, oxazinyl, pyrazinyl (wherein R<sub>a</sub>, R<sub>b</sub>, R<sub>f</sub>, R<sub>3</sub>, R<sub>4</sub> are defined as any of the above embodiments or the preferred embodiments). Said substituent(s) can replace any hydrogen in R<sub>1</sub> group.

In any of the above embodiments, R<sub>2</sub> is preferably cyano; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl; -NR<sub>c</sub>R<sub>d</sub>; -NHC(O)-R<sub>e</sub>; substituted or unsubstituted C<sub>6</sub>-C<sub>10</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl comprising 1-5 heteroatom(s) selected from N, O, and S; or substituted or unsubstituted 5- to 10-membered heterocyclyl comprising 1-5 heteroatom(s) selected from N, O, and S. Specifically, R<sub>2</sub> is selected from substituted or unsubstituted phenyl, naphthyl, pyrrolyl, pyrazolyl, 2H-imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isoxazolyl, oxazolyl, 1,2,4-oxadiazolyl, 2H-pyranyl, 4H-pyranyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, cis(s)-triazinyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 1,4-oxazinyl, morpholinyl, azepinyl, oxapinanyl, 4H-1,2-diazepinyl, indenyl, 2H-indenyl, benzofuranyl, isobenzofuranyl, indolyl, 3H-indolyl, 1H-indolyl, benzooxazolyl, 2H-1-benzopyranyl, quinolinyl, isoquinolinyl, quinazolinyl, 2H-1,4-benzooxazinyl, pyrrolidinyl, pyrrolinyl, quinoxalinyl, furanyl, thienyl, benzoimidazolyl. More preferably, R<sub>2</sub> is selected from substituted or unsubstituted phenyl, naphthyl, pyrazolyl, pyrrolyl, thienyl, pyridinyl, furanyl, tetrahydropyridine, 1,4-benzodioxanyl, isoquinolinyl. The substituent within the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted C<sub>1</sub>-C<sub>5</sub> alkyl or C<sub>1</sub>-C<sub>5</sub> alkyl substituted by halogen or -NR<sub>c</sub>R<sub>d</sub>, C<sub>1</sub>-C<sub>5</sub> alkoxy, C<sub>1</sub>-C<sub>5</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl (wherein R<sub>c</sub>, R<sub>d</sub>, R<sub>e</sub>, R', R'' are as defined above in any of the above embodiments or preferred embodiments). Said substituent may substitute any hydrogen of R<sub>2</sub> group.

In any of the above embodiments, R<sub>3</sub> is preferably halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted C<sub>1</sub>-C<sub>5</sub> alkyl or C<sub>1</sub>-C<sub>5</sub> alkyl substituted by halogen or morpholinyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl. R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R',

or unsubstituted or C<sub>1</sub>-C<sub>5</sub> alkoxy-carbonyl-substituted piperidinyl. R' is C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or unsubstituted 5- to 6-membered heterocyclyl or 5- to 6-membered heterocyclyl substituted by halogen or C<sub>1</sub>-C<sub>5</sub> alkyl. R'' is C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>5</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>5</sub> alkoxy-carbonyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl, or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from halogen, C<sub>1</sub>-C<sub>5</sub> alkyl, and halogen-substituted C<sub>1</sub>-C<sub>5</sub> alkyl. R<sub>a</sub> and R<sub>b</sub> are each independently H or C<sub>1</sub>-C<sub>5</sub> alkyl; R<sub>c</sub> and R<sub>d</sub> are each independently H or C<sub>1</sub>-C<sub>5</sub> alkyl; alternatively, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3-7 membered heterocyclyl; R<sub>e</sub> is unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl or C<sub>6</sub>-C<sub>20</sub> aryl substituted by C<sub>1</sub>-C<sub>6</sub> alkyl or halogen or C<sub>1</sub>-C<sub>6</sub> alkoxy, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4-7 membered heteroaryl (for example, preferably furanyl, pyrrolyl, thienyl).

In a preferred embodiment of this invention, W and V are each independently selected from H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy; X and Z are N, Y is C;



Wherein, R<sub>m</sub> is H, halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxy-carbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), -OC(O)-R<sub>f</sub>, unsubstituted phenyl or phenyl substituted by 1-3 of R<sub>3</sub>, or unsubstituted 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S or 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S which is substituted by 1-3 of R<sub>4</sub>; wherein said heteroaryl is selected from furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranal, pyridinyl, morpholinyl, oxazinyl, pyrazinyl;

25  $R_2$  is cyano; C<sub>1</sub>-C<sub>4</sub> alkoxy-carbonyl; -NR<sub>c</sub>R<sub>d</sub>; -NHC(O)-R<sub>e</sub>; substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5-10 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S; or substituted or unsubstituted

4-10 membered heterocyclyl comprising 1-5 heteroatoms selected from N, O, and S; wherein the substituent(s) in said substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl or C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl substituted by halogen or -NR<sub>c</sub>R<sub>d</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>,  
5 -C(O)R', morpholinyl, morpholinylmethyl, or unsubstituted or R''-substituted piperidinyl;

R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>2</sub> alkylenedioxy; unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or 4-morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', 4-piperidinyl, or 1-t-butoxycarbonyl-4-piperidinyl;

10 R' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or 4-methylpiperazinyl;

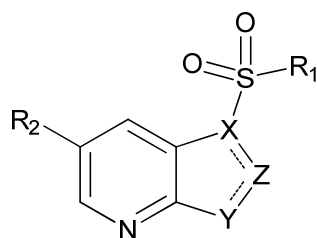
R'' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl, or p-trifluoromethylbenzoyl;

R<sub>a</sub> and R<sub>b</sub> are each independently H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl;

15 R<sub>e</sub> is unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl or C<sub>6</sub>-C<sub>20</sub> aryl substituted by C<sub>1</sub>-C<sub>6</sub> alkyl or halogen or C<sub>1</sub>-C<sub>6</sub> alkoxy, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl or unsubstituted 4-7 membered heteroaryl or 4-7 membered heteroaryl substituted by halogen or C<sub>1</sub>-C<sub>6</sub> alkyl, said 4-7 membered heteroaryl is selected from furanyl, pyrrolyl, thienyl.

20 In another embodiment of this invention, the 5-membered-heterocycle fused pyridine compound has a structure as shown below in formula I:



I

wherein, R<sub>1</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5-10 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S; or substituted or unsubstituted 4-10 membered heterocyclyl comprising 1-5 heteroatoms  
25 selected from N, O, and S; wherein the substituent(s) in the substituted group is halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>

alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), unsubstituted phenyl or phenyl substituted by 1-4 of R<sub>3</sub>, or unsubstituted 4-7 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S or 4-7 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S, which is substituted by 1-4 of R<sub>4</sub>;

R<sub>2</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5-10 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S; or substituted or unsubstituted 4-10 membered heterocyclyl comprising 1-5 heteroatoms selected from N, O, and S; wherein substituent in the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylendioxy, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkyl substituted by halogen or -NR<sub>c</sub>R<sub>d</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl;

wherein R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylendioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl-substituted piperidinyl;

R' is C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>1</sub>-C<sub>6</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4-7 membered heterocyclyl;

R'' is C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>a</sub> and R<sub>b</sub> are independently H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>c</sub> and R<sub>d</sub> are independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; alternatively, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3-7 membered heterocyclyl;

X, Y and Z are independently N or C, and at least one of X, Y and Z is N;

— — — represents single bond or double bond, while X, Y and Z abide by the valence bond theory.

In embodiments described above, preferably, in the compound of Formula I, R<sub>1</sub> is

substituted or unsubstituted C<sub>6</sub>-C<sub>10</sub> aryl; substituted or unsubstituted 5-10 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S; or substituted or unsubstituted 5-10 membered heterocyclyl comprising 1-5 heteroatoms selected from N, O, and S; wherein, substituent(s) in the substituted group is halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, C<sub>1</sub>-C<sub>5</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl, -NR<sub>a</sub>R<sub>b</sub>; -C(O)(NR<sub>a</sub>R<sub>b</sub>), unsubstituted phenyl or phenyl substituted by 1-3 of R<sub>3</sub>, or unsubstituted 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S or 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S substituted by 1-3 of R<sub>4</sub>.

Preferably, in the compound of Formula I, R<sub>2</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>10</sub> aryl; substituted or unsubstituted 5-10 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S; or substituted or unsubstituted 5-10 membered heterocyclyl comprising 1-5 heteroatoms selected from N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted C<sub>1</sub>-C<sub>5</sub> alkyl or C<sub>1</sub>-C<sub>5</sub> alkyl substituted by halogen or -NR<sub>c</sub>R<sub>d</sub>, C<sub>1</sub>-C<sub>5</sub> alkoxy, C<sub>1</sub>-C<sub>5</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl.

Preferably, R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl.

Preferably, R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl-substituted piperidinyl.

Preferably, R' is C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>5</sub> alkyl-substituted 5-6 membered heterocyclyl.

Preferably, R'' is C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>5</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl, or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from halogen, C<sub>1</sub>-C<sub>5</sub> alkyl and halogen-substituted C<sub>1</sub>-C<sub>5</sub> alkyl.

Preferably, R<sub>a</sub> and R<sub>b</sub> are independently H or C<sub>1</sub>-C<sub>5</sub> alkyl;

Preferably, R<sub>c</sub> and R<sub>d</sub> are independently H or C<sub>1</sub>-C<sub>5</sub> alkyl; or, R<sub>c</sub> and R<sub>d</sub>, together

with the N atom to which they are attached, form 3-7 membered heterocyclyl;

Preferably, X, Y and Z are independently N or C, and at least one of X, Y and Z is N, and X, Y and Z abide by valence bond theory. More preferably, said X and Z are N, said Y is C. In another preferred embodiment, said X and Z are C, said Y is N. In another  
5 preferred embodiment, said X is C, said Y and Z are N.

More preferably, in the compound of Formula I, R<sub>1</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>10</sub> aryl, or substituted or unsubstituted 5-10 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S; wherein, the substituent in the substituted group is halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl,  
10 C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), unsubstituted phenyl or phenyl substituted by 1-3 of R<sub>3</sub>; or unsubstituted 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S or 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S substituted by 1-3 of R<sub>4</sub>.

More preferably, in the compound of Formula I, R<sub>2</sub> is substituted or unsubstituted  
15 C<sub>6</sub>-C<sub>10</sub> aryl, substituted or unsubstituted 5-10 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S; or substituted or unsubstituted 5-10 membered heterocyclyl comprising 1-3 heteroatoms selected from N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>2</sub> alkylenedioxy, unsubstituted or halogen or -NR<sub>c</sub>R<sub>d</sub> substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>,  
20 -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl.

More preferably, R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>2</sub> alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl.

More preferably, R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted  
25 C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; or unsubstituted or C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl-substituted piperidinyl.

More preferably, the above R' is C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; or 4-methylpiperazinyl.

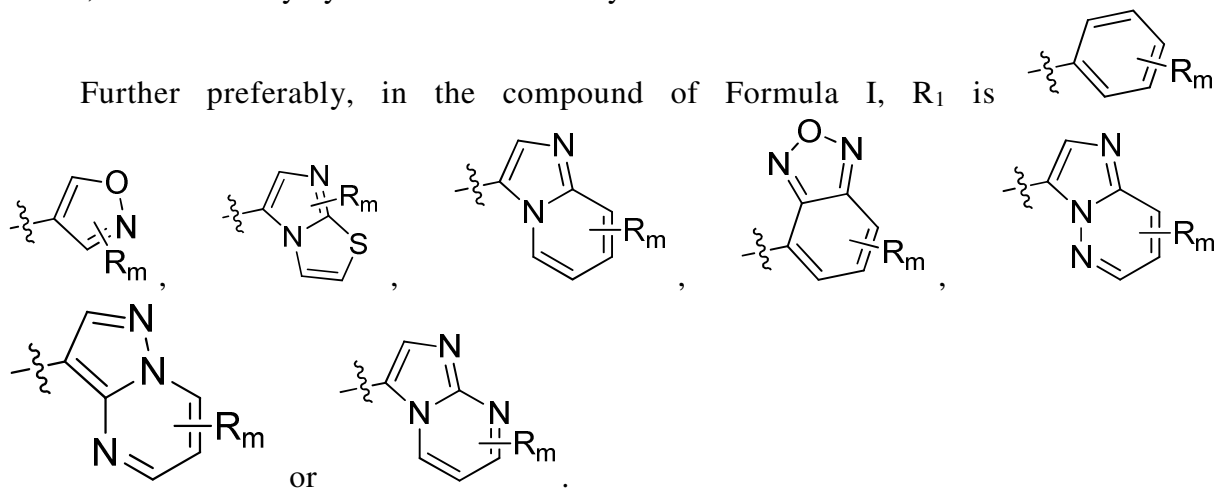
More preferably, the above R'' is C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl;  
30 C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or p-trifluoromethylbenzoyl.

More preferably, the above  $R_a$  and  $R_b$  are independently H or  $C_1$ - $C_4$  alkyl;

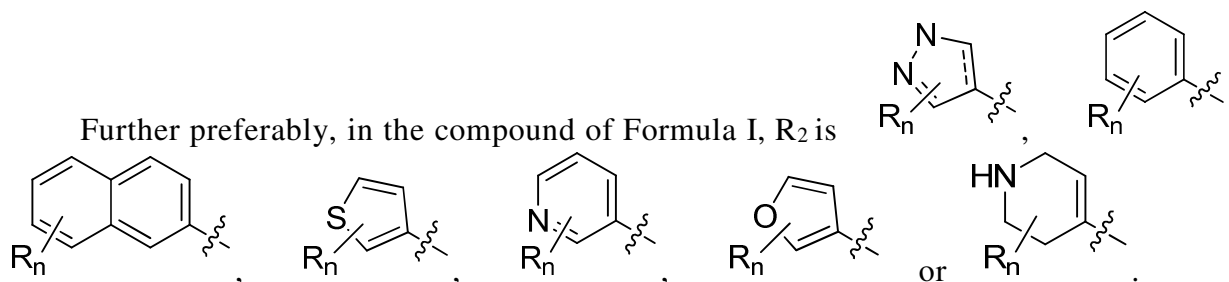
Preferably,  $R_c$  and  $R_d$  are independently H or  $C_1$ - $C_4$  alkyl; or,  $R_c$  and  $R_d$ , together with the N atom to which they are attached, form 3-7 membered heterocyclyl;

More preferably, one or two of the above X, Y and Z are N, while the remaining is C,  
5 and X, Y and Z abide by valence bond theory.

Further preferably, in the compound of Formula I,  $R_1$  is



10 Further preferably, in the compound of Formula I,  $R_2$  is



wherein, the above  $R_m$  is halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylcarbonyl,  $C_1$ - $C_4$  alkoxycarbonyl,  $-NR_aR_b$ ,  $-C(O)(NR_aR_b)$ , unsubstituted phenyl or phenyl substituted by 1-3  
15 of  $R_3$ , or unsubstituted 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S or 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S substituted by 1-3 of  $R_4$ .

The above  $R_n$  is halogen; nitro; cyano;  $C_1$ - $C_2$  alkylenedioxy; unsubstituted or halogen-, dimethylamino-, 4-morpholinyl-, 1-aziridinyl-, 1-azetidiny-,  
20 1-tetrahydropyrrolyl-, 1-piperidinyl- or 1-homopiperidinyl-substituted  $C_1$ - $C_4$  alkyl;  $C_1$ - $C_4$  alkoxy;  $C_1$ - $C_4$  sulfamido;  $-NR_aR_b$ ;  $-C(O)R'$ ; 4-morpholinyl; or unsubstituted or  $R''$ -substituted piperidinyl;

wherein, the above  $R_3$  is halogen, nitro, cyano,  $C_1$ - $C_2$  alkylenedioxy, unsubstituted

or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or 4-morpholinyl;

the above R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; 4-piperidinyl; or 1-t-butoxy-4-piperidinyl;

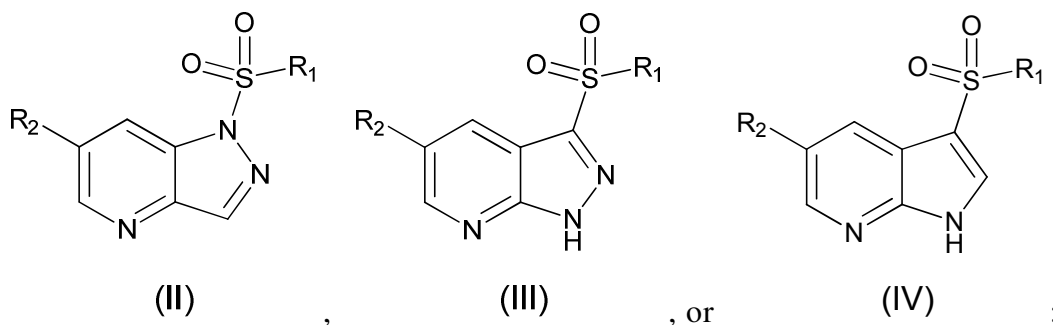
5 the above R' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or 4-methylpiperazinyl;

the above R'' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl, or p-trifluoromethylbenzoyl;

the above R<sub>a</sub> and R<sub>b</sub> are independently H or C<sub>1</sub>-C<sub>4</sub> alkyl .

In this specification, R<sub>m</sub> refers to the corresponding substituent in R<sub>1</sub> group, R<sub>n</sub> refers to the corresponding substituent in R<sub>2</sub> group. In R<sub>1</sub> group, there may be 1, 2, 3 or more identical or various R<sub>m</sub> substituents. In R<sub>2</sub> group, there may be 1, 2, 3 or more identical or various R<sub>n</sub> substituents. In one preferred embodiment, when R<sub>1</sub> is C<sub>6</sub>-C<sub>20</sub> aryl, 5-10 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S, or 4-10 membered heterocyclyl comprising 1-5 heteroatoms selected from N, O, and S, it is desirable to have substituent R<sub>m</sub> therein in the 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-position of said aryl, heteroaryl, heterocyclyl (with the proviso that there is hydrogen atom available for substitution in said position). When R<sub>2</sub> is C<sub>6</sub>-C<sub>20</sub> aryl, 5-10 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S, or 4-10 membered heterocyclyl comprising 1-5 heteroatoms selected from N, O, and S, it is desirable to have substituent R<sub>n</sub> therein in the 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-position of said aryl, heteroaryl, heterocyclyl (with the proviso that there is hydrogen atom available for substitution in said position). In a further preferred embodiment, R<sub>1</sub> and/or R<sub>2</sub> have polycyclic structure, R<sub>m</sub> and/or R<sub>n</sub> substituent attached to positions in the cyclic structure different from where the sulfonyl is attached.

25 Preferably, the 5-member-heterocycle fused pyridine compound of Formula I is following 5-member-heterocycle fused pyridine compounds as shown in Formulae (II), (III), and (IV),



wherein,  $R_1$  and  $R_2$  are as defined above.

Therefore, in any of the above embodiments, preferably, said 5-member-heterocycle fused pyridine compound has a structure as shown above in Formula II, wherein:

5  $R_1$  is selected from phenyl, naphthyl, isoxazolyl, 8-10 membered bicyclic heteroaryl comprising 2-3 heteroatoms selected from N, O, and S (such as imidazo[2,1-b]thiazolyl, imidazo[1,2-a]pyridinyl, benzo[1,2,5]oxadiazolyl, imidazo[1,2-b]pyridazinyl, pyrazolo[1,5-a]imidazolyl, imidazo[1,2-a]pyrimidinyl, etc.). Substituent in the substituted group is halogen; nitro; hydroxyl; cyano; unsubstituted or halogen- or  
10 morpholinyl-substituted  $C_1$ - $C_5$  alkyl;  $C_1$ - $C_5$  alkoxy;  $C_1$ - $C_5$  alkylcarbonyl;  $C_1$ - $C_5$  alkoxy carbonyl;  $-NR_aR_b$ ;  $-C(O)(NR_aR_b)$ ;  $-OC(O)-R_f$ ; unsubstituted phenyl or phenyl substituted by 1-3 of  $R_3$ ; or unsubstituted 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S or 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S substituted by 1-3 of  $R_4$ , wherein said heteroaryl is  
15 preferably furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranal, pyridinyl, morpholinyl, oxazinyl, pyrazinyl;

$R_2$  is cyano;  $C_1$ - $C_4$  alkoxy carbonyl;  $-NR_cR_d$ ;  $-NHC(O)-R_e$ ; substituted or unsubstituted  $C_6$ - $C_{10}$  aryl; substituted or unsubstituted 5-10 membered heteroaryl comprising 1-5 heteroatoms selected from N, O, and S; or substituted or unsubstituted  
20 5-10 membered heterocyclyl comprising 1-5 heteroatoms selected from N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano,  $C_1$ - $C_4$  alkylendioxy; unsubstituted  $C_1$ - $C_5$  alkyl or  $C_1$ - $C_5$  alkyl substituted by halogen or  $-NR_cR_d$ ;  $C_1$ - $C_5$  alkoxy;  $C_1$ - $C_5$  sulfamido;  $-NR_aR_b$ ;  $-C(O)R'$ ; morpholinyl; or unsubstituted or  $R''$ -substituted piperidinyl;

25  $R_3$  is halogen; nitro; cyano;  $C_1$ - $C_4$  alkylendioxy; unsubstituted or halogen- or morpholinyl-substituted  $C_1$ - $C_5$  alkyl;  $C_1$ - $C_5$  alkoxy;  $-NR_aR_b$ ;  $-C(O)R'$ ; or morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>5</sub> alkyl; C<sub>1</sub>-C<sub>5</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; or unsubstituted or C<sub>1</sub>-C<sub>5</sub> alkoxy-carbonyl-substituted piperidinyl;

R' is C<sub>1</sub>-C<sub>5</sub> alkyl; C<sub>1</sub>-C<sub>5</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; or unsubstituted or halogen- or C<sub>1</sub>-C<sub>5</sub> alkyl-substituted 5-6 membered heterocyclyl;

R'' is C<sub>1</sub>-C<sub>5</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>5</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>5</sub> alkoxy-carbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from halogen, C<sub>1</sub>-C<sub>5</sub> alkyl, halogen-substituted C<sub>1</sub>-C<sub>5</sub> alkyl;

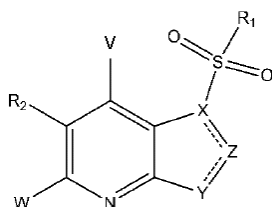
R<sub>a</sub> and R<sub>b</sub> are independently H or C<sub>1</sub>-C<sub>5</sub> alkyl;

R<sub>c</sub> and R<sub>d</sub> are independently H or C<sub>1</sub>-C<sub>5</sub> alkyl; or, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3-7 membered heterocyclyl.

R<sub>e</sub> is unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkyl- or halogen- or C<sub>1</sub>-C<sub>6</sub> alkoxy-substituted C<sub>6</sub>-C<sub>20</sub> aryl, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4-7 membered heteroaryl.

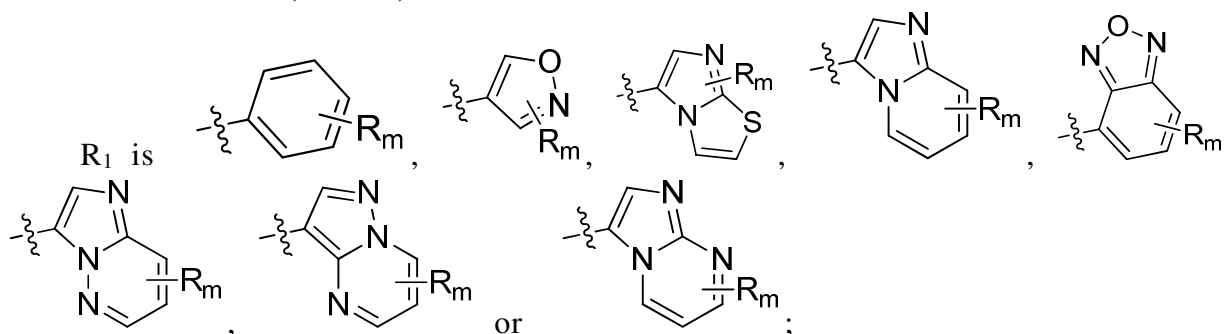
In another embodiment of this invention, said 5-member-heterocycle fused pyridine compound has a structure as shown below in Formula (X),

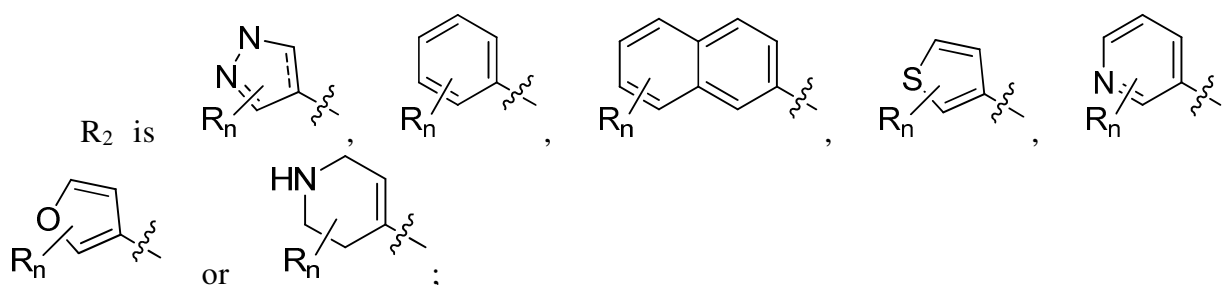


(X)

wherein, W and V are independently selected from hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy;

X and Z are N, Y is C;





wherein, R<sub>m</sub> is H, halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl; -NR<sub>a</sub>R<sub>b</sub>; -C(O)(NR<sub>a</sub>R<sub>b</sub>); -OC(O)-R<sub>f</sub>; unsubstituted phenyl or phenyl substituted by 1-3 of R<sub>3</sub>; or unsubstituted 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S or 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S substituted by 1-3 of R<sub>4</sub>, wherein said heteroaryl is selected from furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranal, pyridinyl, morpholinyl, oxazinyl, pyrazinyl;

R<sub>n</sub> is H, halogen, nitro, cyano, C<sub>1</sub>-C<sub>2</sub> alkylenedioxy; unsubstituted or halogen-, dimethylamino-, 4-morpholinyl-, 1-aziridinyl-, 1-azetidyl-, 1-tetrahydropyrrolyl-, 1-piperidinyl- or 1-homopiperidinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> sulfamido; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; 4-morpholinyl; or unsubstituted or R''-substituted piperidinyl;

R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>2</sub> alkylenedioxy; unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; or 4-morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; 4-piperidinyl; or 1-t-butoxycarbonyl-4-piperidinyl;

R' is C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; or 4-methylpiperazinyl;

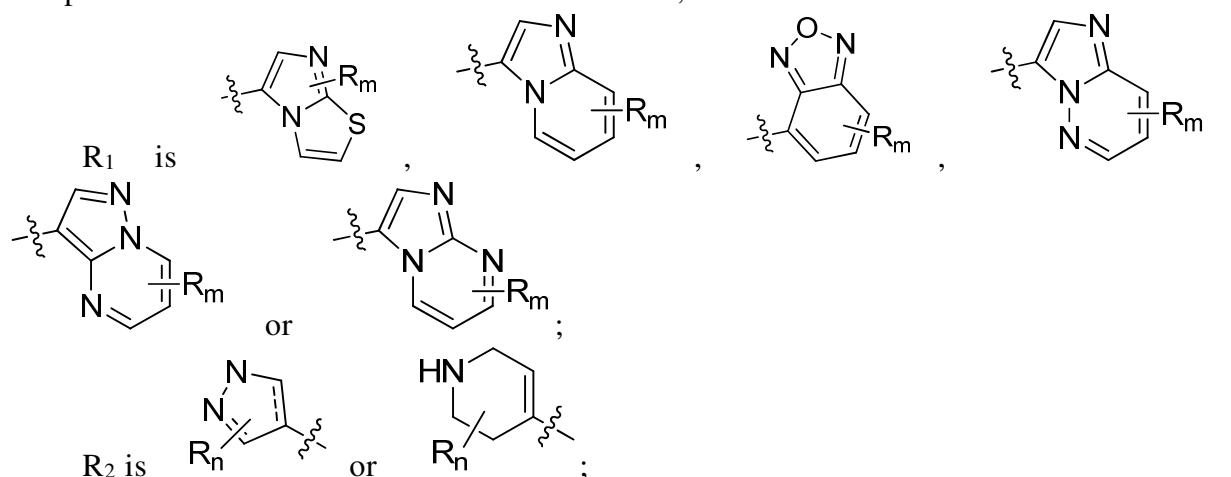
R'' is C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or p-trifluoromethylbenzoyl;

R<sub>a</sub> and R<sub>b</sub> are independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl;

R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4-7 membered heteroaryl, said 4-7 membered heteroaryl is selected from furanyl, pyrrolyl, thienyl.

In another embodiment of this invention, said 5-member-heterocycle fused pyridine

compound has a structure as shown in Formula II, wherein:



5 wherein,  $R_m$  is H, halogen, nitro, cyano,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylcarbonyl,  $C_1$ - $C_4$  alkoxy carbonyl;

$R_n$  is H, halogen; nitro; cyano;  $C_1$ - $C_2$  alkylenedioxy; unsubstituted or halogen-, dimethylamino-, 4-morpholinyl-, 1-aziridinyl-, 1-azetidyl-, 1-tetrahydropyrrolyl-, 1-piperidinyl- or 1-homopiperidinyl-substituted  $C_1$ - $C_4$  alkyl;  $C_1$ - $C_4$  alkoxy;  $C_1$ - $C_4$  sulfamido;  $-NR_aR_b$ ;  $-C(O)R'$ ; 4-morpholinyl; or unsubstituted or  $R''$ -substituted piperidinyl;

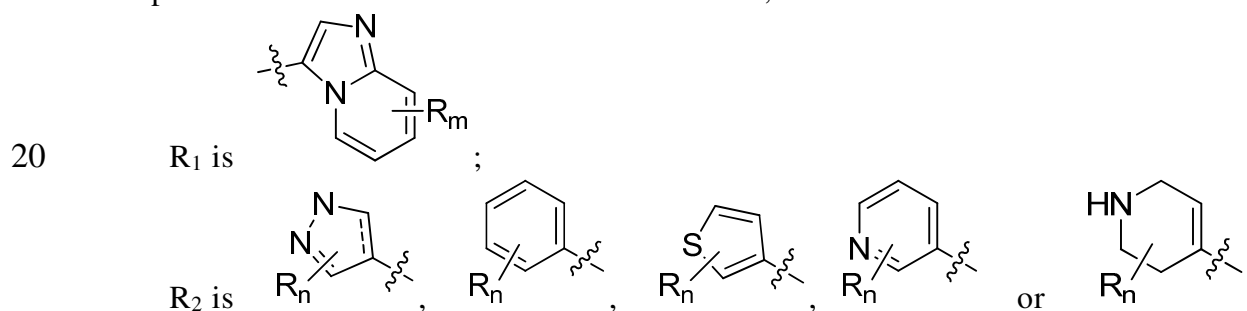
$R'$  is  $C_1$ - $C_4$  alkyl;  $C_1$ - $C_4$  alkoxy;  $-NR_aR_b$ ; or 4-methylpiperazinyl;

$R''$  is  $C_1$ - $C_4$  alkyl;  $C_3$ - $C_6$  cycloalkyl;  $C_1$ - $C_4$  alkylcarbonyl;  $C_1$ - $C_4$  alkoxy carbonyl;  $C_3$ - $C_6$  cycloalkylcarbonyl; or p-trifluoromethylbenzoyl;

15  $R_a$  and  $R_b$  are independently H,  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkylcarbonyl;

$R_f$  is  $C_1$ - $C_6$  alkyl, or unsubstituted or halogen- or  $C_1$ - $C_6$  alkyl-substituted 4-7 membered heteroaryl.

In another embodiment of this invention, said 5-member-heterocycle fused pyridine compound has a structure as shown in Formula II, wherein:



wherein,  $R_m$  is H, halogen; nitro; hydroxyl;  $C_1$ - $C_4$  alkoxy; unsubstituted phenyl or phenyl substituted by 1-3 of  $R_3$ ; or unsubstituted 5-7 membered heteroaryl comprising 1-3

heteroatoms selected from N, O, and S or 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S substituted by 1-3 of R<sub>4</sub>, wherein said heteroaryl is selected from furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranlyl, pyridinyl, morpholinyl, oxazinyl, pyrazinyl;

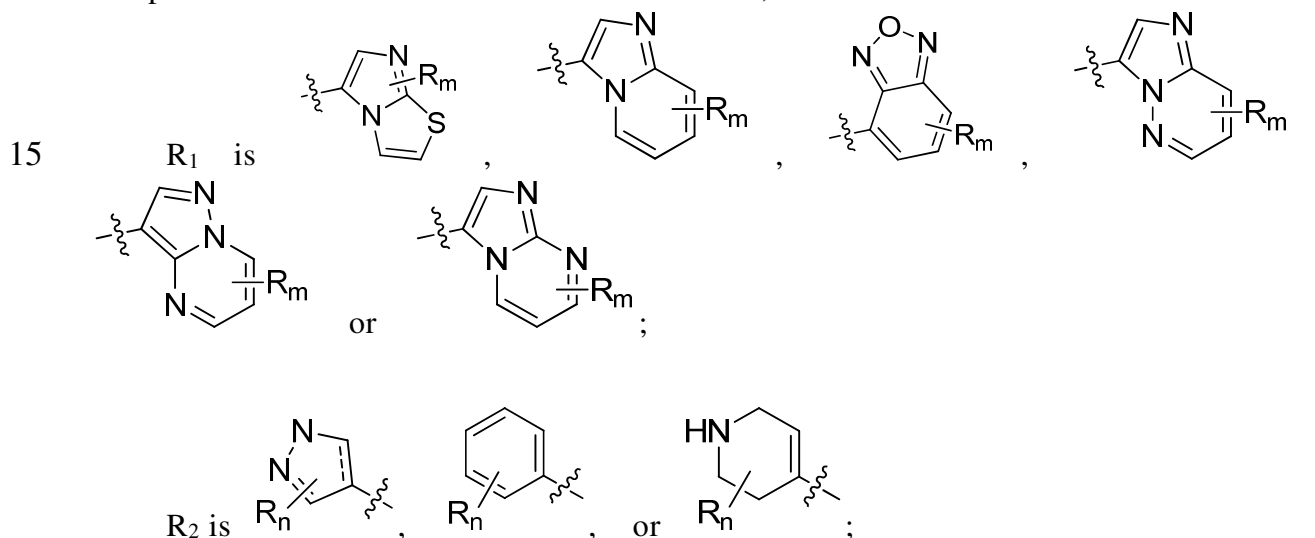
5 R<sub>n</sub> is H, halogen, nitro, cyano unsubstituted or halogen-, dimethylamino-, 4-morpholinyl-, 1-aziridinyl-, 1-azetidiny-, 1-tetrahydropyrrolyl-, 1-piperidinyl- or 1-homopiperidinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> sulfamido; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; 4-morpholinyl; or unsubstituted or R''-substituted piperidinyl;

R' is C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; or 4-methylpiperazinyl;

10 R'' is C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or p-trifluoromethylbenzoyl;

R<sub>a</sub> and R<sub>b</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl.

In another embodiment of this invention, said 5-member-heterocycle fused pyridine compound has a structure as shown in Formula II, wherein:



wherein, R<sub>m</sub> is H, halogen; nitro; cyano; unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl; -NR<sub>a</sub>R<sub>b</sub>; -C(O)(NR<sub>a</sub>R<sub>b</sub>); -OC(O)-R<sub>f</sub>; unsubstituted phenyl or phenyl substituted by 1-3 of R<sub>3</sub>; or unsubstituted 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S or 5-7 membered heteroaryl comprising 1-3 heteroatoms selected from N, O, and S substituted by 1-3 of R<sub>4</sub>, wherein said heteroaryl is selected from furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranlyl, pyridinyl, morpholinyl, oxazinyl, pyrazinyl;

25

R<sub>n</sub> is H, halogen; unsubstituted or halogen-, dimethylamino-, 4-morpholinyl-, 1-aziridinyl-, 1-azetidiny-, 1-tetrahydropyrrolyl-, 1-piperidinyl- or 1-homopiperidinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> sulfamido; -C(O)R'; 4-morpholinyl; or unsubstituted or R''-substituted piperidinyl;

5 R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>2</sub> alkylendioxy; unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; or 4-morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; 4-piperidinyl; or 1-t-butoxycarbonyl-4-piperidinyl;

R' is C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; -NR<sub>a</sub>R<sub>b</sub>; or 4-methylpiperazinyl;

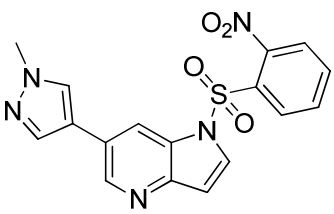
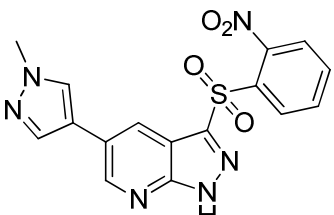
10 R'' is C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or p-trifluoromethylbenzoyl;

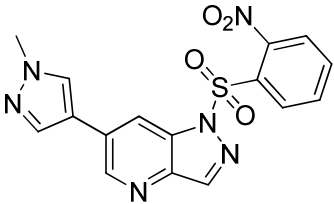
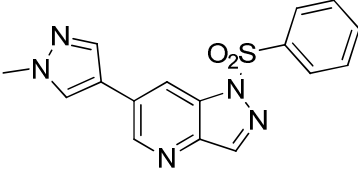
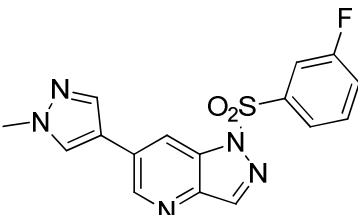
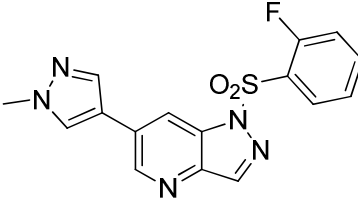
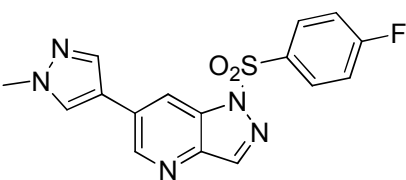
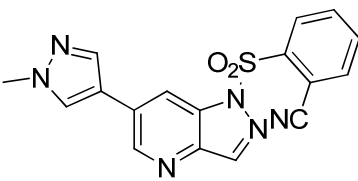
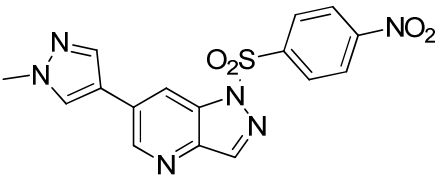
R<sub>a</sub> and R<sub>b</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl;

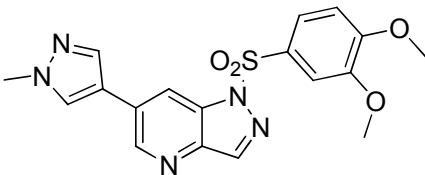
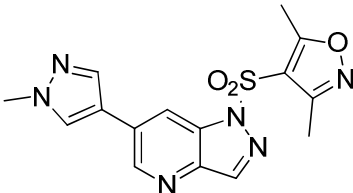
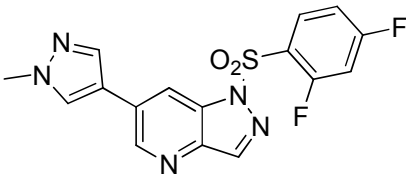
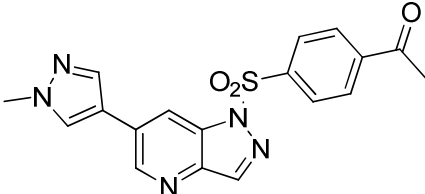
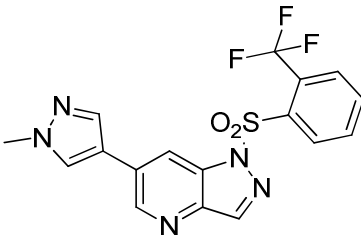
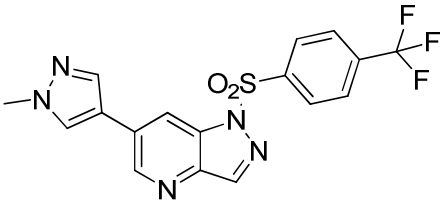
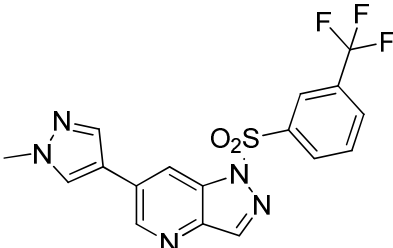
R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4-7 membered heteroaryl, said 4-7 membered heteroaryl is selected from furanyl, pyrrolyl, 15 thienyl.

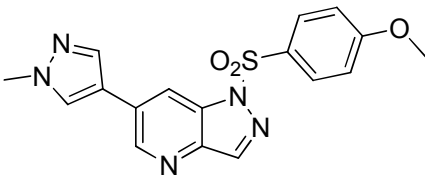
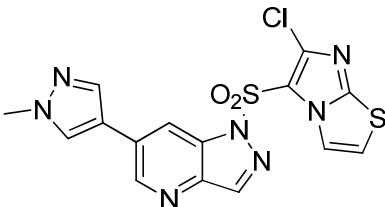
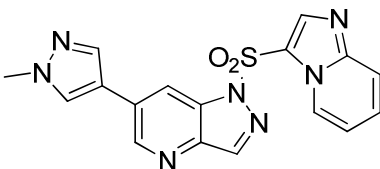
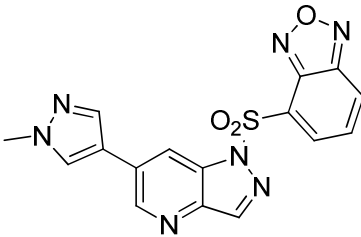
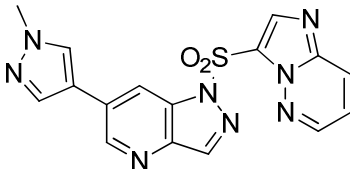
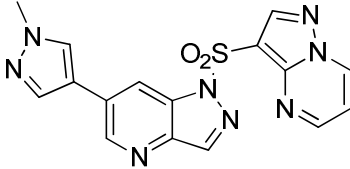
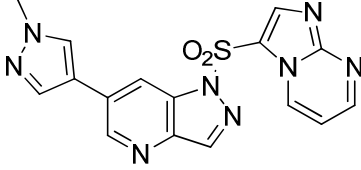
A person skilled in the art will appreciate that, any of the embodiments described above, including any preferred embodiments or more preferred embodiment, may combine with each other in any way to form new technical solutions, such technical solutions shall be considered as within the scope of explicit description provided herein.

20 In preferred embodiment of this invention, said 5-member-heterocycle fused pyridine compound is a compound selected from the following compound:

| No. | Compound                                                                          | Structure                                                                            |
|-----|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 01  | 1-(2-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrrolo[3,2-b]pyridine  |  |
| 02  | 3-(2-nitrobenzenesulfonyl)-5-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[3,4-b]pyridine |  |

|    |                                                                                    |                                                                                      |
|----|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 03 | 1-(2-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine  |    |
| 04 | 1-benzenesulfonyl-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine           |    |
| 05 | 1-(3-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |    |
| 06 | 1-(2-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 07 | 1-(4-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 08 | 1-(2-cyanobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine  |  |
| 09 | 1-(4-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine  |  |

|    |                                                                                             |                                                                                      |
|----|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 10 | 1-(3,4-dimethoxybenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine     |    |
| 11 | 1-(3,5-dimethylisoxazolsulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine     |    |
| 12 | 1-(2,4-difluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine      |    |
| 13 | 1-(4-acetylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine          |  |
| 14 | 1-(2-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 15 | 1-(4-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 16 | 1-(3-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |

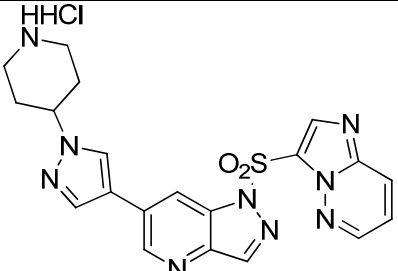
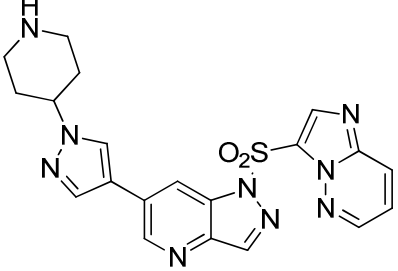
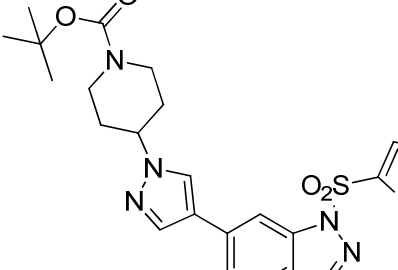
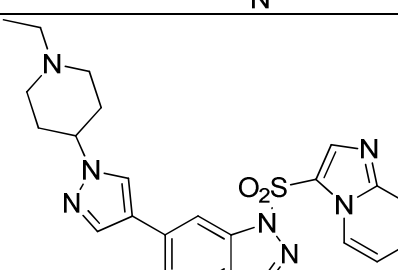
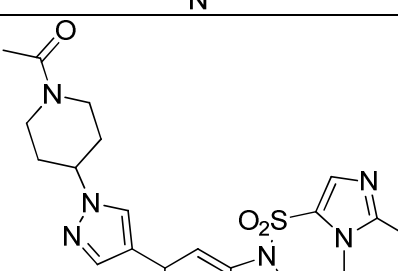
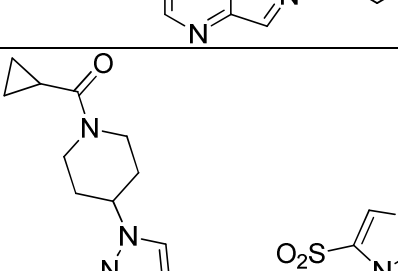
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|----|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 17 | 1-(4-methoxybenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                     |    |
| 18 | 1-[(6-chloro-imidazo[2,1-b]thiazole)-5-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |    |
| 19 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine            |    |
| 20 | 1-(benzo[1,2,5]oxadiazole-4-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine            |   |
| 21 | 1-(imidazo[1,2-b]pyridazine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine          |  |
| 22 | 1-(pyrazolo[1,5-a]pyrimidine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine         |  |
| 23 | 1-(imidazo[1,2-a]pyrimidine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine          |  |

|    |                                                                                                                           |  |
|----|---------------------------------------------------------------------------------------------------------------------------|--|
| 24 | 1-[(6-chloro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                   |  |
| 25 | 1-[(6-chloro-imidazo[1,2-b]pyridazine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                 |  |
| 26 | 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine          |  |
| 27 | 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 28 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-phenyl-1-H-pyrazolo[4,3-b]pyridine                                                |  |
| 29 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(3-thienyl)-1-H-pyrazolo[4,3-b]pyridine                                           |  |
| 30 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(3-pyridinyl)-1-H-pyrazolo[4,3-b]pyridine                                         |  |

|    |                                                                                                                            |  |
|----|----------------------------------------------------------------------------------------------------------------------------|--|
| 31 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(3-furanyl)-1-H-pyrazolo[4,3-b]pyridine                                            |  |
| 32 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-trifluoromethylphenyl)-1-H-pyrazolo[4,3-b]pyridine                              |  |
| 33 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(2-naphthyl)-1-H-pyrazolo[4,3-b]pyridine                                           |  |
| 34 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-methylsulfamidophenyl)-1-H-pyrazolo[4,3-b]pyridine                              |  |
| 35 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[(1-t-butoxycarbonyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine |  |
| 36 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[6-(1,4-benzodioxanyl)]-1-H-pyrazolo[4,3-b]pyridine                                |  |
| 37 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-1-H-pyrazolo[4,3-b]pyridine              |  |

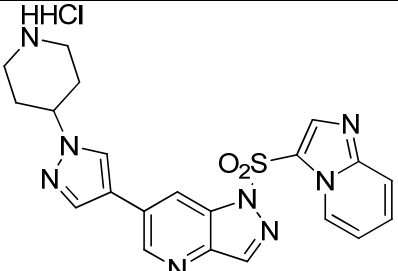
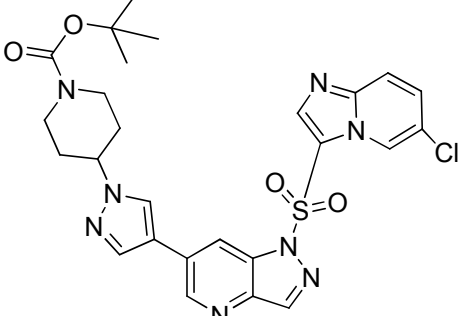
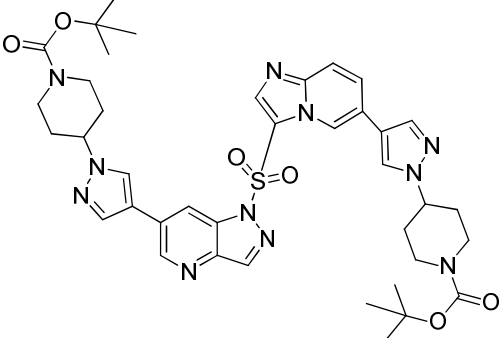
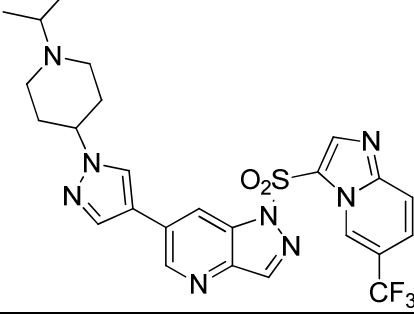
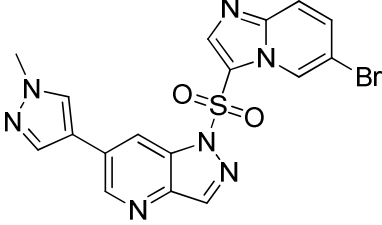
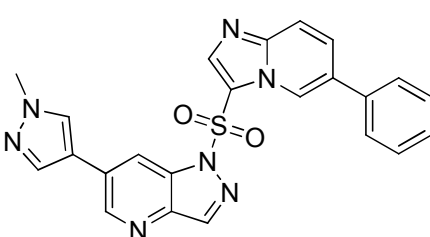
|    |                                                                                                     |  |
|----|-----------------------------------------------------------------------------------------------------|--|
| 38 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-morpholinomethylphenyl)-1-H-pyrazolo[4,3-b]pyridine      |  |
| 39 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-morpholinylphenyl)-1-H-pyrazolo[4,3-b]pyridine           |  |
| 40 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-acetylphenyl)-1-H-pyrazolo[4,3-b]pyridine                |  |
| 41 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-dimethylaminocarbonylphenyl)-1-H-pyrazolo[4,3-b]pyridine |  |
| 42 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-dimethylaminophenyl)-1-H-pyrazolo[4,3-b]pyridine         |  |
| 43 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(2,5-dimethoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine           |  |

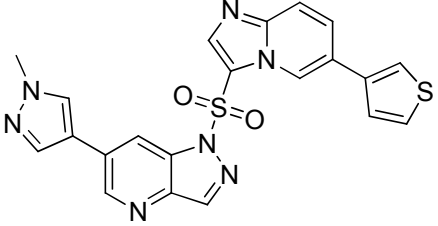
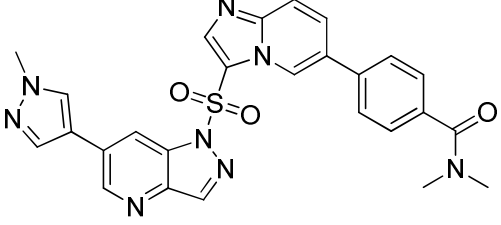
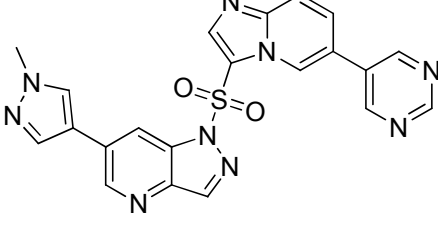
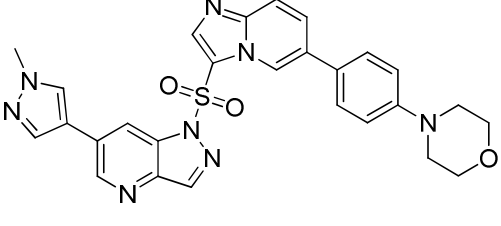
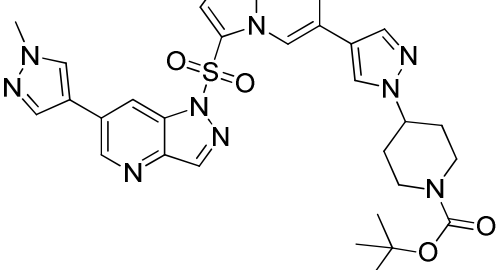
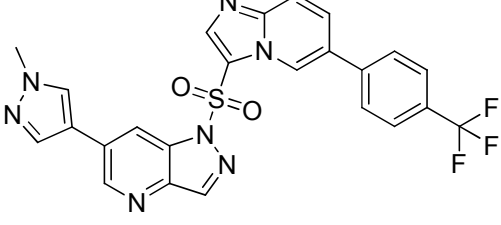
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| 44 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{ { 1-[(1-t-butoxycarbonyl)-4-piperidinyl] }-4-pyrazolyl }-1-H-pyrazolo[4,3-b]pyridine    |  |
| 45 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{ [1-(4-piperidinyl)]-4-pyrazolyl }-1-H-pyrazolo[4,3-b]pyridine                           |  |
| 46 | 1-(pyrazolo[1,5-a]pyrimidine-3-sulfonyl)-6-{ { 1-[(1-t-butoxycarbonyl)-4-piperidinyl] }-4-pyrazolyl }-1-H-pyrazolo[4,3-b]pyridine |  |
| 47 | 1-(imidazo[1,2-a]pyrimidine-3-sulfonyl)-6-{ [1-(4-piperidinyl)]-4-pyrazolyl }-1-H-pyrazolo[4,3-b]pyridine                         |  |
| 48 | 1-[(6-chloro-imidazo[2,1-b]thiazole)-5-sulfonyl]-6-{ [1-(4-piperidinyl)]-4-pyrazolyl }-1-H-pyrazolo[4,3-b]pyridine                |  |
| 49 | 1-(imidazo[1,2-b]pyridazine-3-sulfonyl)-6-{ { 1-[(1-t-butoxycarbonyl)-4-piperidinyl] }-4-pyrazolyl }-1-H-pyrazolo[4,3-b]pyridine  |  |

|    |                                                                                                                               |                                                                                      |
|----|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 50 | 1-(imidazo[1,2-b]pyridazine-3-sulfonyl)-6-{{1-(4-piperidinyl)}-4-pyrazolyl}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine chloride |    |
| 51 | 1-(imidazo[1,2-b]pyridazine-3-sulfonyl)-6-{{1-(4-piperidinyl)}-4-pyrazolyl}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine          |    |
| 52 | 1-(imidazo[1,2-a]pyrimidine-3-sulfonyl)-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine  |   |
| 53 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-ethyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine               |  |
| 54 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-acetyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine              |  |
| 55 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopropylcarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine |  |

|    |                                                                                                                               |  |
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| 56 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopentylcarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine |  |
| 57 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclohexylcarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine  |  |
| 58 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-p-trifluoromethyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine   |  |
| 59 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-isopropyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine           |  |
| 60 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopentyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine         |  |

|    |                                                                                                                                                                                               |  |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| 61 | 1-[(6-chloro-imidazo[1,2-b]pyridazine)-3-sulfonyl]-6-{ { 1-[(1-t-butoxycarbonyl)-4-piperidinyl] }-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine                                                    |  |
| 62 | 1-{(6-{ { 1-[(1-t-butoxycarbonyl)-4-piperidinyl] }-4-pyrazolyl}-imidazo[1,2-b]pyridazine)-3-sulfonyl}-6-{ { 1-[(1-t-butoxycarbonyl)-4-piperidinyl] }-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine |  |
| 63 | 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{ { 1-[(1-t-butoxycarbonyl)-4-piperidinyl] }-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine                                             |  |
| 64 | 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{ [ 1-(4-piperidinyl)]-4-pyrazolyl }-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine chloride                                            |  |
| 65 | 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{ [ 1-(4-piperidinyl)]-4-pyrazolyl }-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine                                                     |  |

|    |                                                                                                                                                                                     |                                                                                      |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 66 | 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-(4-piperidinyl)-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine chloride                                                                       |    |
| 67 | 1-[(6-chloro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine                                                |    |
| 68 | 1-{{6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]-4-pyrazolyl}-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine |   |
| 69 | 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{{1-[(1-isopropyl)-4-piperidinyl]-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine                                              |  |
| 70 | 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                                                                              |  |
| 71 | 1-[(6-phenyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                                                                             |  |

|    |                                                                                                                                                         |                                                                                      |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 72 | 1- {[6-(3-thiophene)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                                         |    |
| 73 | 1- {[6-(4-dimethylaminocarbonylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                       |    |
| 74 | 1- {[6-(5-pyrimidine)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                                        |    |
| 75 | 1- {[6-(4-morpholinylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                                 |  |
| 76 | 1- {(6-{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 77 | 1- {[6-(4-trifluoromethylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                             |  |

|    |                                                                                                                                             |  |
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| 78 | 1-{{6-(3-fluoro-4-methylphenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                  |  |
| 79 | 1-{{6-(4-isopropoxyphenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                       |  |
| 80 | 1-{{6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine  |  |
| 81 | 1-{{6-(4-fluorophenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                           |  |
| 82 | 1-{{6-([1-(4-piperidinyl)]-4-pyrazolyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine chloride |  |
| 83 | 1-{{6-(3-trifluoromethylphenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                  |  |

|    |                                                                                                                             |  |
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| 84 | 1- {[6-(2-trifluoromethylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 85 | 1- {[6-(4-dimethylaminophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine   |  |
| 86 | 1- {[6-(3-fluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine          |  |
| 87 | 1- {[6-(2,4-difluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine      |  |
| 88 | 1- {[6-(3,4,5-trifluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine   |  |
| 89 | 1- {[6-(4-methoxyphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine         |  |
| 90 | 1- {[6-(4-methylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine          |  |

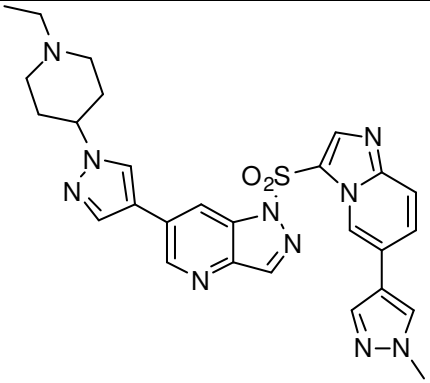
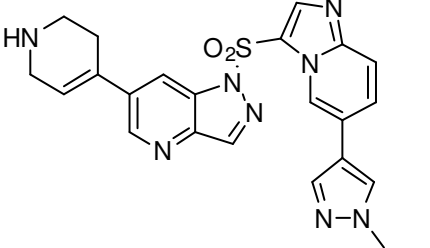
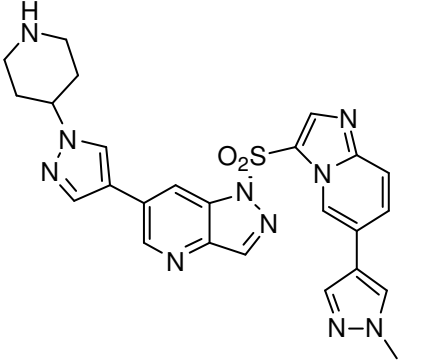
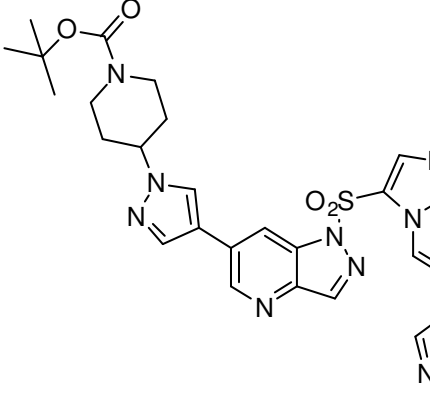
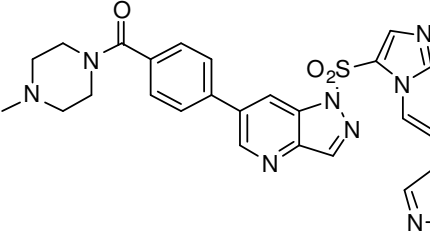
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| 91 | 1-{{6-(4-morpholinomethylphenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 92 | 1-{{6-(4-cyanophenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine            |  |
| 93 | 1-{{6-[6-(1,4-benzodioxanyl)]-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine    |  |
| 94 | 1-{{6-(4-chlorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine           |  |
| 95 | 1-{{6-(3-fluoro-4-pyridinyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine     |  |
| 96 | 1-{{6-(3,4-dimethoxyphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine      |  |

|     |                                                                                                                                                      |  |
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| 97  | 1- {[6-(2-methoxyphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                                  |  |
| 98  | 1- {[6-[5-(1,2-methylenedioxyphenyl)]-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                     |  |
| 99  | 1- {[6-(2-fluoro-5-pyridinyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                             |  |
| 100 | 1- {[6-(3-cyanophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine                                    |  |
| 101 | 1- {(6-(3-fluoro-4-methylaminocarbonylphenyl)-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine             |  |
| 102 | 1- {(6-(3-fluoro-4-methylaminocarbonylphenyl)-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(2-dimethylaminoethyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 118 | 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-fluorophenyl)-1-H-pyrazolo[4,3-b]pyridine                                                       |  |

|     |                                                                                                               |  |
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| 119 | 1-[(6-n-butylamino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 120 | 1-[(6-acetylamino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine  |  |
| 121 | 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine      |  |
| 122 | 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-isoquinolonyl)-1-H-pyrazolo[4,3-b]pyridine             |  |
| 123 | 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(6-methoxy-2-naphthyl)-1-H-pyrazolo[4,3-b]pyridine        |  |
| 124 | 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-morpholinylphenyl)-1-H-pyrazolo[4,3-b]pyridine         |  |
| 125 | 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3-trifluoromethylphenyl)-1-H-pyrazolo[4,3-b]pyridine     |  |

|     |                                                                                                                  |  |
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| 126 | 1-[(6-hydroxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-methoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine                |  |
| 127 | 1-[(6-hydroxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-phenyl-1-H-pyrazolo[4,3-b]pyridine                           |  |
| 128 | 1-[(6-isobutyryloxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine   |  |
| 129 | 1-[(6-furan-2-acyloxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine |  |
| 130 | 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-ethoxycarbonyl-1-H-pyrazolo[4,3-b]pyridine                     |  |
| 131 | 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-benzamido-1-H-pyrazolo[4,3-b]pyridine                          |  |
| 132 | 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-propionamido-1-H-pyrazolo[4,3-b]pyridine                       |  |

|     |                                                                                                                                                    |  |
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| 133 | 1-{{6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-benzamido-1-H-pyrazolo[4,3-b]pyridine                                         |  |
| 134 | 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3-methoxybenzamido)-1-H-pyrazolo[4,3-b]pyridine                                               |  |
| 135 | 1-{{6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-cyclopentyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine |  |
| 136 | 1-{{6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{{1-[(1-cyclopentyl)-4-piperidinyl]}}-4-pyrazolyl-1-H-pyrazolo[4,3-b]pyridine |  |
| 137 | 1-{{6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-isopropyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine   |  |

|     |                                                                                                                                                           |                                                                                      |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 138 | 1-{{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{{1-[(1-ethyl)-4-piperidinyl]}-4-pyrazolyl}}-1-H-pyrazolo[4,3-b]pyridine            |    |
| 139 | 1-{{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine                       |    |
| 140 | 1-{{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{{1-(4-piperidinyl)}-4-pyrazolyl}}-1-H-pyrazolo[4,3-b]pyridine                      |   |
| 141 | 1-{{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}}-1-H-pyrazolo[4,3-b]pyridine |  |
| 142 | 1-{{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[4-(4-methylpiperazine-1-carbonyl)phenyl]}-1-H-pyrazolo[4,3-b]pyridine              |  |

|     |                                                                                                                                                |  |
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| 143 | 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-(4-morpholinomethylphenyl)-1-H-pyrazolo[4,3-b]pyridine                    |  |
| 144 | 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-phenyl-1-H-pyrazolo[4,3-b]pyridine                                        |  |
| 145 | 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{[1-(1-isopropyl)-4-piperidinyl]-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine |  |

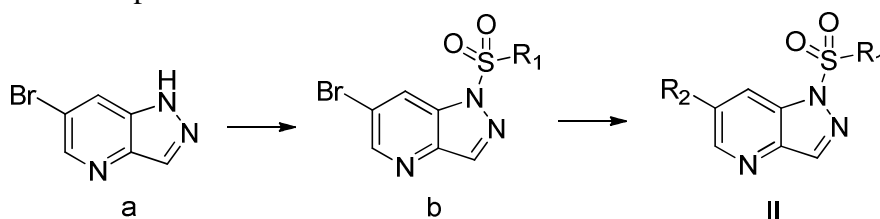
The pharmaceutical salt of said 5-member-heterocycle fused pyridine compound according to the present invention can be produced by reacting the compound of Formula (X) with inorganic acid or organic acid, wherein said inorganic acid includes hydrochloride, hydrobromide, phosphoric acid, sulphuric acid and others, said organic acid includes ascorbic acid, nicotinic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, oxalic acid, malic acid, glycolic acid, succinic acid, propionic acid, acetic acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and others.

The pharmaceutical salt of said 5-member-heterocycle fused pyridine compound according to the present invention can be produced by dissolving said compound into alcohol solution saturated by corresponding acid and carrying out the reaction, for instance, the 5-member-heterocycle fused pyridine compound of this invention may be dissolved by saturated HCl solution in dioxane, stirring for 30 minutes at room temperature, filtering to obtain the resultant hydrochloride salt.

Furthermore, the compound of this invention may have one or more chiral centers. In this circumstance, the compound of this invention also covers individual diastereomer, racemate, as well as individual R and S enantiomer. In this specification, when a racemate mixture is disclosed, two optical isomers (including diastereomer and enantiomer) or stereoisomers each substantially free of the other isomer are explicitly disclosed and claimed at the same time.

Another goal of this invention is to provide a process for the production of said 5-member-heterocycle fused pyridine compound, said process produces the 5-member-heterocycle fused pyridine compound by reaction paths shown in the schemes below, which may comprise steps as following;

Reaction path I:



1) Reacting a starting compound a, synthesized referring to prior patent applications (WO2012056372; WO2010056999; WO201208778), with corresponding sulfonyl chloride under the action of a base to produce a compound of Formula b.

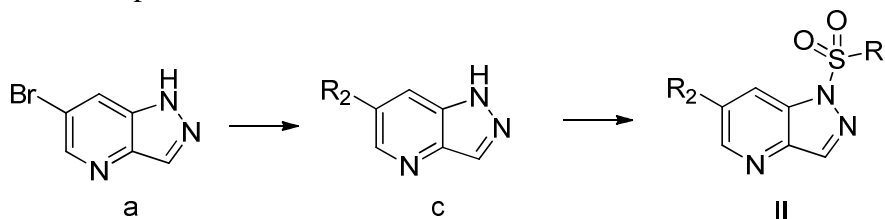
2) Reacting the compound of Formula b with corresponding boric acid or boric acid ester in a coupling reaction catalyzed by metal catalyst and under the action of a base, such that a compound of Formula II is produced.

Wherein, R<sub>1</sub> and R<sub>2</sub> are defined as above;

In step 1) described above, the suitable reaction condition, for the sulfonamide condensation reaction between said corresponding sulfonyl chloride and the starting compound a, is a routine choice for a person skilled in the art. Generally, methanol, ethanol, dioxane, tetrahydrofuran, methylene chloride, chloroform and others may be chosen as the solvent. The base is well known to a person skilled in the art, non-limiting examples include triethylamine, sodium hydroxide, potassium hydroxide, sodium hydride, potassium t-butoxide, and others. In step 2) described above, the suitable condition for the coupling reaction involving the compound of Formula b is a routine choice for a person

skilled in the art. The metal catalyst is well known to a person skilled in the art, non-limiting examples include 1,1'-Bis (diphenylphosphino) ferrocene palladium (II) dichloride, tetrakis (triphenylphosphine) palladium (0), bis (acetonitrile) palladium (II) chloride, and others. The base is a base well known to a person skilled in the art,  
5 non-limiting examples include  $\text{Cs}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{K}_3\text{PO}_4$ ,  $\text{NaHCO}_3$  and others.

Reaction path II:

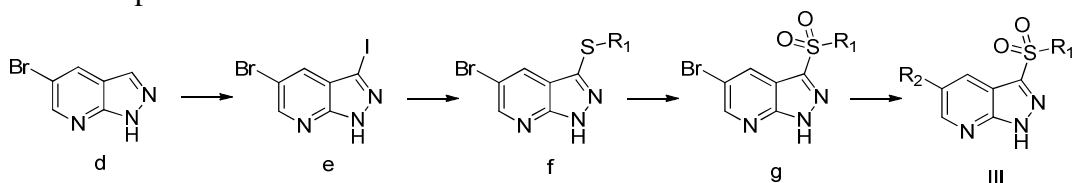


1) Reacting a starting compound a, synthesized referring to prior patent applications (WO2012056372; WO2010056999; WO201208778), with corresponding boric acid or  
10 boric acid ester in a coupling reaction catalyzed by metal catalyst and under the action of a base, such that a compound of Formula c is produced.

2) Reacting the compound of Formula c with corresponding sulfonyl chloride under the action of a base to produce a compound of Formula II.

In step 1) described above, the suitable condition for the coupling reaction involving  
15 the compound of Formula a and corresponding boric acid or boric acid ester is a routine choice for a person skilled in the art. The metal catalyst is well known to a person skilled in the art, non-limiting examples include 1,1'-Bis (diphenylphosphino) ferrocene palladium (II) dichloride, tetrakis (triphenylphosphine) palladium (0), bis (acetonitrile) palladium (II) dichloride, and others. The base is a base well known to a person skilled in  
20 the art, non-limiting examples include  $\text{Cs}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{K}_3\text{PO}_4$ ,  $\text{NaHCO}_3$  and others. In step 2) described above, the suitable reaction condition, for the sulfonamide condensation reaction between said corresponding sulfonyl chloride and the compound of Formula c, is a routine choice for a person skilled in the art. Generally, methanol, ethanol, dioxane, tetrahydrofuran, methylene chloride, chloroform and others may be chosen as the  
25 solvent. The base is well known to a person skilled in the art, non-limiting examples include triethylamine, sodium hydroxide, potassium hydroxide, sodium hydride, potassium t-butoxide, and others.

Reaction path III:



1) Subjecting starting compound d to halogenation reaction with iodine under the action of a base to produce a compound e;

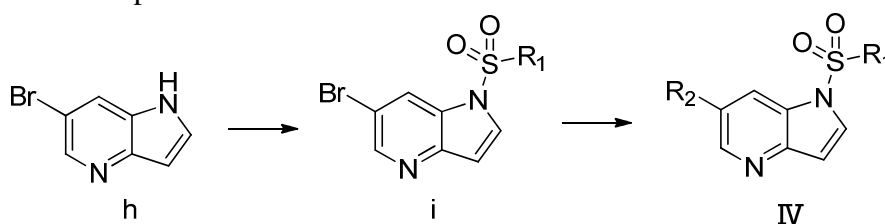
5      2) Subjecting the compound e to a metal-catalyzed coupling reaction with corresponding thiol compound to produce the compound of Formula f;

3) Subjecting the compound of Formula f to oxidation under the action of an oxidizer to produce a compound of Formula g;

4) Subjecting the compound of Formula g to a metal-catalyzed coupling reaction  
10 with corresponding boric acid or boric acid ester to produce the compound of Formula III;

wherein, R<sub>1</sub> and R<sub>2</sub> are defined as above;

Reaction path IV:

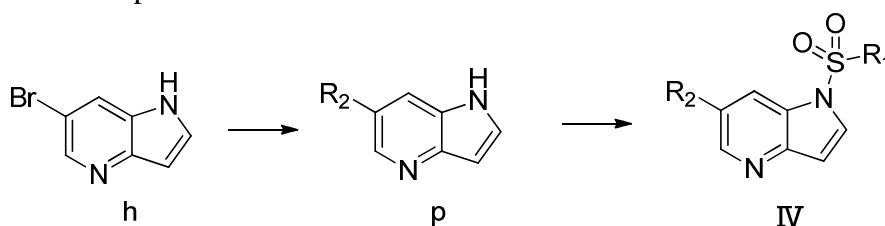


15      1) Reacting a starting compound h with corresponding sulfonyl chloride under the action of a base to produce a compound of Formula i.

2) Subjecting the compound of Formula i to a metal-catalyzed coupling reaction with corresponding boric acid or boric acid ester under the action of a base to produce a compound of Formula IV;

20      wherein, R<sub>1</sub> and R<sub>2</sub> are defined as above.

Reaction path V:



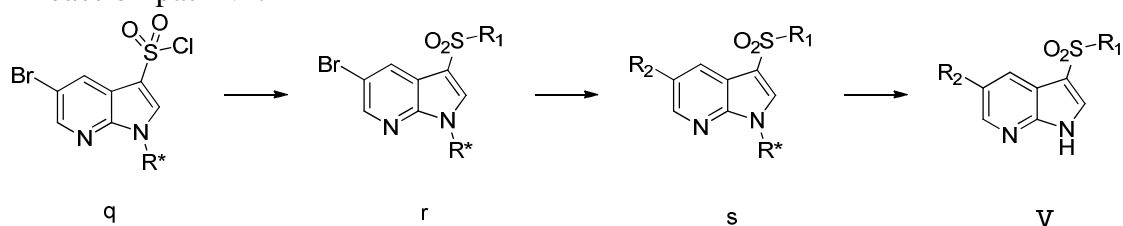
1) Subjecting a starting compound h to a metal-catalyzed coupling reaction with

corresponding boric acid or boric acid ester under the action of a base to produce a compound of Formula p;

2) Reacting the compound of Formula p with corresponding sulfonyl chloride under the action of a base to produce a compound of Formula IV;

5 wherein,  $R_1$  and  $R_2$  are defined as above.

Reaction path VI:



1) Reacting a starting compound q having a protection group  $R^*$  with corresponding amine under the action of a base to produce compound r.

10 2) Subjecting the compound of Formula r to a metal-catalyzed coupling reaction with corresponding boric acid or boric acid ester under the action of a base to produce a compound of Formula s;

3) Removing the protection group from the compound of Formula s to produce a compound of Formula V.

15 Wherein,  $R_1$  and  $R_2$  are defined as above. The  $R^*$  is a protection group for N atom that is well known to a person skilled in the art, non-limiting examples include t-butoxycarbonyl, 2-nitrobenzenesulfonyl, benzyl, and others.

The scope of this invention covers any new intermediates disclosed herein as well.

20 In a third aspect, this invention provides a pharmaceutical composition comprising a prophylactically or therapeutically effective amount of any one of the 5-member-heterocycle fused pyridine compound described above, one or more of pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, and a pharmaceutically acceptable excipient. The term “prophylactically or therapeutically  
25 effective amount” refers to an amount of the compound that is sufficient to induce the desired prophylactic or therapeutic effect, such as inhibiting protein lysine kinase and/or anti-tumor activity, while the particular amount will vary with factors known to a person skilled in the art, such as the physical and chemical properties of the compound, and

characteristics of the vehicle, as well as the dosing regime to be applied. Moreover, the pharmaceutical composition of this invention may further comprise other active agents, such as other lysine kinase inhibitor and/or antitumor substance, for an improved effect.

Pharmaceutically acceptable excipients suitable for this invention include, for example, saccharides, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and cocoa bean oil; polyols, such as propylene glycol, glycerine, sorbitol, mannitol and polyethylene glycol; alginic acid; emulsifiers, such as Tween; wetting agents, such as sodium dodecyl sulfate; coloring agents; flavoring agents; tableting agent; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solution.

The pharmaceutical composition of this invention can be administrated in any conventional dosage and mode.

The 5-member-heterocycle fused pyridine compound, pharmaceutical acceptable salts thereof, pharmaceutical acceptable solvates thereof, or pharmaceutical composition as described above can be used to prevent or treat disorders associated with abnormal cell proliferation, morphological change and hyperkinesis related to abnormal *in vivo* protein tyrosine kinase, or diseases associated with angiogenesis or cancer metastasis, particularly, diseases associated with the over-expression or over-activation of receptor protein tyrosine kinase c-Met, such as liver cancer, bile duct cancer, pancreatic cancer, lung cancer, thyroid cancer, pleural mesothelioma, lung cancer, stomach cancer, breast cancer, colon cancer, prostate cancer, pancreatic cancer, esophageal cancer, ovarian cancer, renal cancer, glioma, melanoma, etc.

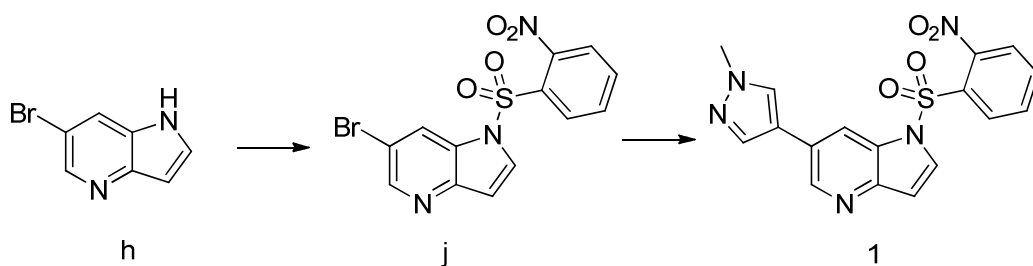
Therefore, in another aspect, this invention is further related to a method for preventing or treating disorders associated with abnormal cell proliferation, morphological change and hyperkinesis related to abnormal *in vivo* protein tyrosine kinase, and diseases related to angiogenesis or metastasis in an individual in need thereof, said method comprises administering a prophylactically or therapeutically effective amount of

the compound or pharmaceutical composition of this invention to said individual. In a preferred embodiment, the diseases are associated with the over-expression or over-activation of receptor protein tyrosine kinase c-Met. More preferably, said disease is selected from cancers associated with the over-expression or over-activation of receptor protein tyrosine kinase c-Met, such as liver cancer, bile duct cancer, pancreatic cancer, lung cancer, thyroid cancer, pleural mesothelioma, lung cancer, stomach cancer, breast cancer, colon cancer, prostate cancer, pancreatic cancer, esophageal cancer, ovarian cancer, renal cancer, glioma, and melanoma.

The following examples are provided to specifically describe the preparation of the compounds of this invention, and their biological activity as inhibitor against tyrosine kinase, particularly c-Met, but this invention is not limited to these examples.

H-NMR measurements were made on Bruker AMX-300 or 400. Microwave irradiation was carried out using Biotage Initiator Microwave Reactor. All solvents for reactions are purified according to routine methods. Silica gel (200-300 mesh or 300-400 mesh) for column chromatography was manufactured by Branch of Qingdao Haiyang Chemical Co., Ltd. Flash preparative chromatography was performed on Parallel Frac FR-260 of YAMAZEN, Japan. Thin layer chromatography plate and preparative plate HSGF-254 is manufactured by Jiangyou Silica Development Co., Ltd. of Yantai. All solvents were of analytical grade solvents. All reagents were purchased from Sinopharm Chemical Reagent Co., Ltd. Color development was performed by means of iodine, ultraviolet fluorescence, and others. Removing organic solvent by evaporation under reduced pressure was performed in a rotary evaporator.

Example 1: Preparation of 1-(2-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrrolo[3,2-b]pyridine



#### Step 1: Preparation of compound j

Sixty five milligrams of sodium anhydride was dissolved into 15 ml anhydrous tetrahydrofuran, stirred for 5 minutes at room temperature. One hundred and sixty milligrams of compound h was dissolved into 15 ml anhydrous tetrahydrofuran, then slowly and dropwisely added into tetrahydrofuran solution of sodium hydride, stirred for 30 minutes at room temperature after the addition was completed. One hundred and ninty eight milligrams of 2-nitrophenylsulfonyl chloride was dissolved into 15 ml anhydrous tetrahydrofuran, then slowly and dropwisely added into reaction solution, stirred overnight at room temperature after the addition was completed, the reaction was then completed. Tetrahydrofuran was removed by evaporation, the remainder was dissolved into dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound j (m=256 mg, yield: 82%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64 (d,  $J = 2.0$  Hz, 1H), 8.34 (d,  $J = 1.3$  Hz, 1H), 7.92 (d,  $J = 7.4$  Hz, 1H), 7.86 – 7.79 (m, 3H), 7.79 – 7.73 (m, 1H), 6.93 (d,  $J = 3.9$  Hz, 1H).

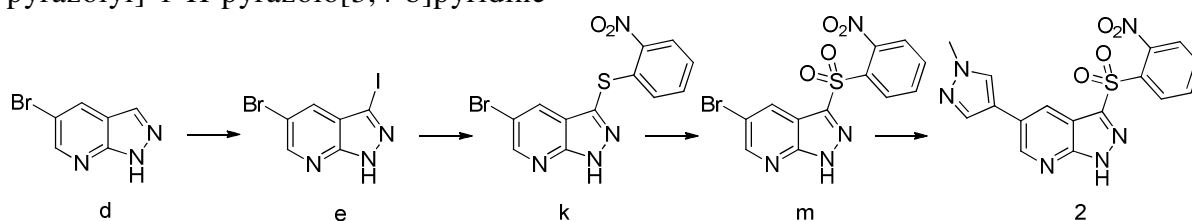
#### Step 2: Preparation of 1-(2-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrrolo[3,2-b]pyridine

Into a microwave reaction tube were disposed 80 mg compound j, 65 mg 1-methyl-1H-pyrazolo-4-borate pinacol ester and 87 mg potassium carbonate, into the microwave reaction tube were added 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water, air was displaced for three times, under a nitrogen atmosphere, 8.5 mg complex of 1,1'-bis(diphenylphosphino) ferrocene palladium (II) dichloride and dichloromethane was added into said microwave tube, then the microwave tube was sealed and placed in microwave reactor, reaction was conducted at a temperature of 120°C for 30 minutes, till

the reaction was completed. The reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound 1 (m=62 mg, yield: 77%).

<sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  8.87 (d,  $J$  = 1.5 Hz, 1H), 8.38 (s, 1H), 8.27 (d,  $J$  = 8.4 Hz, 1H), 8.21 (d,  $J$  = 1.8 Hz, 1H), 8.13 (d,  $J$  = 7.8 Hz, 1H), 8.05 (s, 1H), 8.00 (d,  $J$  = 3.7 Hz, 2H), 7.92 (t,  $J$  = 7.9 Hz, 1H), 7.06 (d,  $J$  = 3.5 Hz, 1H), 3.91 (s, 3H).

Example 2: Preparation of 3-(2-nitrobenzenesulfonyl)-5-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[3,4-b]pyridine



Step 1: Preparation of compound e

Four grams of compound d and 10.25 g of iodine were dissolved into 50 ml N,N-dimethylformamide, stirred for 5 minutes at room temperature. Slowly, 2.83 g of potassium hydroxide was added into the above solution, and further stirred at room temperature for 3 hours, the reaction was completed. The reactant liquid was poured into 1000 ml water, solid was precipitated, filtered, the filter cake was washed three times by water immersion, vacuum dried to obtain compound e (m=1.35 g, yield: 41.3%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.47 (d,  $J$  = 2.1 Hz, 1H), 7.93 (d,  $J$  = 2.1 Hz, 1H).

Step 2: Preparation of compound k

Into 30 ml isopropanol, 1.5 g of compound e, 1.44 g of 2-nitrophenylsulfonyl chloride, 88 mg cuprous iodide and 516 ml glycol were dissolved, air was displaced for three times, heated at 140°C to react overnight under a nitrogen atmosphere. After the reaction was completed, the reactant liquid was cooled to room temperature, added 250ml of dichloromethane, and filtered. The filtrate was washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound k (m=832 mg, yield: 51.2%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.69 (d,  $J$  = 2.2 Hz, 1H), 8.30 (d,  $J$  = 9.7 Hz, 1H),

8.14 (d,  $J = 2.1$  Hz, 1H), 7.32 (t,  $J = 8.6$  Hz, 2H), 6.82 (d,  $J = 7.9$  Hz, 1H).

Step 3: Preparation of compound m

Into 20 ml trichloromethane, 612 mg compound k and 601 mg m-chloroperbenzoic acid was dissolved, stirred at room temperature for 3 hours, the reaction was completed.

5 The reactant liquid was diluted by 30 ml dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound m (m=268 mg, yield: 40.1%).

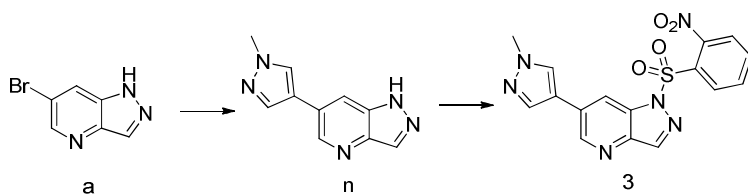
$^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.82 (d,  $J = 2.2$  Hz, 1H), 8.53 (d,  $J = 2.2$  Hz, 1H),  
10 8.46 – 8.42 (m, 1H), 8.10 – 8.06 (m, 1H), 8.05 – 7.99 (m, 2H).

Step 4: Preparation of 3-(2-nitrobenzenesulfonyl)-5-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[3,4-b]pyridine

Into a microwave reaction tube, 70 mg compound 15, 57 mg 1-methyl-1H-pyrazolo-4-borate pinacol ester and 76 mg potassium carbonate were  
15 disposed, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 7.5 mg complex of 1,1'-bis(diphenylphosphino) ferrocene palladium (II) dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reaction was conducted at a  
20 temperature of 120°C for 30 minutes, till the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound 2 (m=58 mg, yield: 83%).

25  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  9.03 (d,  $J = 2.0$  Hz, 1H), 8.47 - 8.44 (m, 1H), 8.41 (s, 1H), 8.40 (d,  $J = 2.1$  Hz, 1H), 8.08 (s, 1H), 8.07 - 8.05 (m, 1H), 8.01 (m, 2H), 3.92 (s, 3H).

Example 3: Preparation of 1-(2-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine:



#### Step 1: Preparation of compound n

Into a microwave reaction tube, 300 mg compound a, 473 mg 1-methyl-1H-pyrazolo-4-borate pinacol ester and 628 mg potassium carbonate were disposed, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 62 mg complex of 1,1'-bis(diphenylphosphino) ferrocene palladium (II) dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed, The microwave tube was placed into a microwave reactor, reaction was conducted at a temperature of 120°C for 30 minutes, till the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain compound n (m=275 mg, yield: 91%).

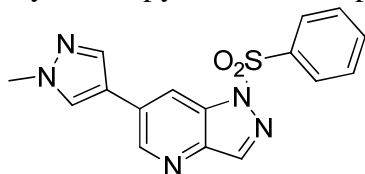
$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.29 (s, 1H), 8.80 (s, 1H), 8.36 (s, 1H), 8.24 (s, 1H), 8.07 (s, 2H), 3.90 (s, 3H).

#### Step 2: Preparation of 1-(2-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

Sixty five mg sodium hydride was dissolved into 15 ml anhydrous DMF, stirred for 5 minutes at room temperature. One hundred and sixty mg compound n was dissolved in 15 ml anhydrous DMF, then slowly and dropwisely added into sodium hydride solution in DMF, and stirred for 30 minutes at room temperature after the addition was finished. One hundred and ninty eight mg 2-nitrophenylsulfonyl chloride was dissolved in 15 ml anhydrous DMF, slowly and dropwisely added into reaction solution, stirred overnight at room temperature after the addition was finished, till the reaction was completed. DMF was removed by evaporation, the remainder was dissolved into dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound 3 (m=256 mg, yield: 82%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.90 (d,  $J = 1.9$  Hz, 1H), 8.47 – 8.42 (m, 1H), 8.41 (d,  $J = 0.9$  Hz, 1H), 8.38 (dd,  $J = 1.9, 0.9$  Hz, 1H), 7.96 (d,  $J = 0.7$  Hz, 1H), 7.88 (s, 1H), 7.87 – 7.82 (m, 2H), 7.80 – 7.72 (m, 1H), 4.03 (s, 3H).

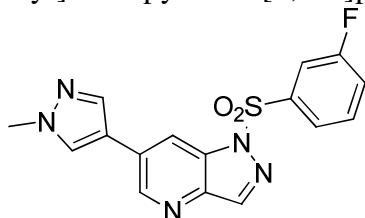
Example 4: Preparation of 1-benzenesulfonyl-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for phenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-benzenesulfonyl-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.84 (d,  $J = 1.7$  Hz, 1H), 8.49 (s, 1H), 8.38 (s, 1H), 8.02 (d,  $J = 7.4$  Hz, 2H), 7.94 (s, 1H), 7.86 (s, 1H), 7.62 (t,  $J = 7.4$  Hz, 1H), 7.51 (t,  $J = 7.8$  Hz, 2H), 4.03 (s, 3H).

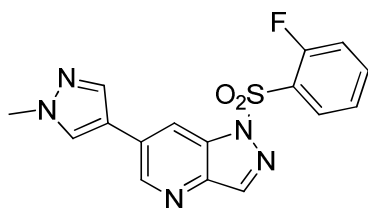
Example 5: Preparation of 1-(3-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3-fluorophenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(3-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.86 (s, 1H), 8.46 (s, 1H), 8.40 (s, 1H), 7.94 (s, 1H), 7.91 – 7.78 (m, 2H), 7.72 (d,  $J = 7.4$  Hz, 1H), 7.54 – 7.41 (m, 1H), 7.32 (s, 1H), 4.03 (s, 3H).

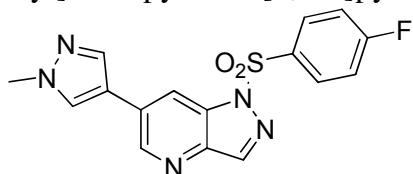
Example 6: Preparation of 1-(2-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 2-fluorophenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(2-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (d,  $J = 1.9$  Hz, 1H), 8.52 (s, 1H), 8.38 (d,  $J = 0.8$  Hz, 1H), 8.24 - 8.15 (m, 1H), 7.95 (d,  $J = 0.7$  Hz, 1H), 7.86 (s, 1H), 7.64 (dd,  $J = 8.3, 3.2$  Hz, 1H), 7.43 - 7.33 (m, 2H), 7.17 - 7.07 (m, 1H), 4.03 (s, 3H).

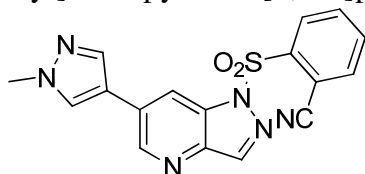
Example 7: Preparation of 1-(4-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-fluorophenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(4-fluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.85 (d,  $J = 1.9$  Hz, 1H), 8.47 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.38 (d,  $J = 0.9$  Hz, 1H), 8.09 - 8.01 (m, 2H), 7.94 (d,  $J = 0.8$  Hz, 1H), 7.85 (s, 1H), 7.23 - 7.14 (m, 2H), 4.03 (s, 3H).

Example 8: Preparation of 1-(2-cyanobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

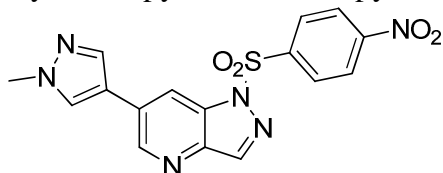


Except for 2-cyanophenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(2-cyanobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process

as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.89 (d,  $J = 1.9$  Hz, 1H), 8.71 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.42 (dd,  $J = 8.3, 1.1$  Hz, 1H), 8.39 (d,  $J = 0.9$  Hz, 1H), 7.96 (d,  $J = 0.7$  Hz, 1H), 7.89 (s, 1H), 7.81 (m, 3H), 4.01 (s, 3H).

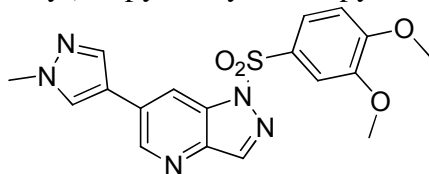
5        Example 9: Preparation of 1-(4-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-nitrophenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(4-nitrobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.87 (d,  $J = 1.9$  Hz, 1H), 8.49 - 8.38 (m, 2H), 8.38 - 8.31 (m, 2H), 8.26 - 8.18 (m, 2H), 7.95 (d,  $J = 0.7$  Hz, 1H), 7.86 (s, 1H), 4.04 (s, 3H).

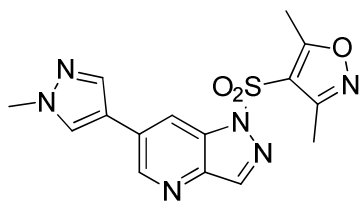
15        Example 10: Preparation of 1-(3,4-dimethoxybenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3,4-dimethoxyphenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(3,4-dimethoxybenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.84 (d,  $J = 1.9$  Hz, 1H), 8.48 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.37 (d,  $J = 0.9$  Hz, 1H), 7.94 (d,  $J = 0.8$  Hz, 1H), 7.86 (s, 1H), 7.63 (dd,  $J = 8.6, 2.2$  Hz, 1H), 7.46 (d,  $J = 2.2$  Hz, 1H), 6.89 (d,  $J = 8.7$  Hz, 1H), 4.03 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H).

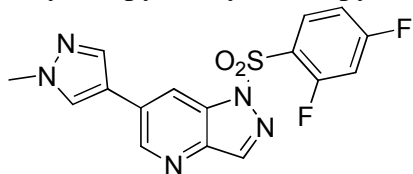
25        Example 11: Preparation of 1-(3,5-dimethylisoxazolesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3,5-dimethylisoxazolesulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(3,5-dimethylisoxazolesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (d,  $J = 1.8$  Hz, 1H), 8.46 – 8.38 (m, 2H), 7.92 (s, 1H), 7.84 (s, 1H), 4.03 (s, 3H).

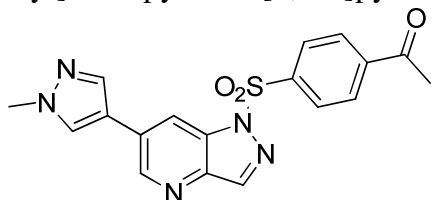
Example 12: Preparation of 1-(2,4-difluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 2,4-difluorophenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(2,4-difluorobenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.89 (d,  $J = 1.6$  Hz, 1H), 8.50 (s, 1H), 8.38 (s, 1H), 8.23 (dd,  $J = 14.3, 8.4$  Hz, 1H), 7.95 (s, 1H), 7.86 (s, 1H), 7.10 (t,  $J = 8.4$  Hz, 1H), 6.87 (t,  $J = 9.2$  Hz, 1H), 4.03 (s, 3H).

Example 13: Preparation of 1-(4-acetylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

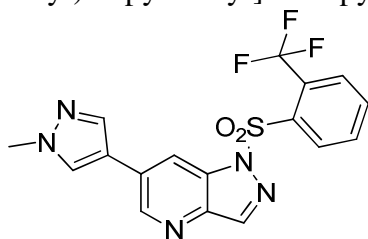


Except for 4-acetylphenylsulfonyl chloride, compound 1-(4-acetylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.86 (d,  $J = 1.9$  Hz, 1H), 8.48 (dd,  $J = 1.9, 0.9$  Hz,

1H), 8.39 (d,  $J = 0.8$  Hz, 1H), 8.14 – 8.09 (m, 2H), 8.06 – 8.02 (m, 2H), 7.95 (s, 1H), 7.86 (s, 1H), 4.03 (s, 3H).

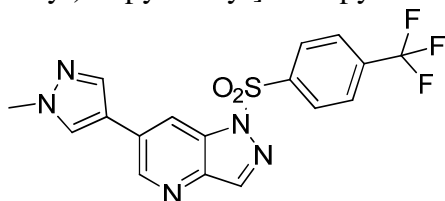
Example 14: Preparation of 1-(2-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 2-trifluoromethylphenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(2-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.87 (d,  $J = 1.9$  Hz, 1H), 8.50 – 8.46 (m, 2H), 8.36 (d,  $J = 0.8$  Hz, 1H), 7.94 (s, 1H), 7.91 – 7.87 (m, 1H), 7.86 – 7.80 (m, 3H), 4.03 (s, 3H).

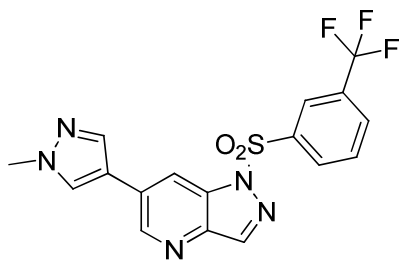
Example 15: Preparation of 1-(4-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-trifluoromethylphenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(4-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.86 (d,  $J = 1.9$  Hz, 1H), 8.47 (d,  $J = 1.0$  Hz, 1H), 8.40 (d,  $J = 0.8$  Hz, 1H), 8.15 (d,  $J = 8.2$  Hz, 2H), 7.94 (s, 1H), 7.86 (s, 1H), 7.77 (d,  $J = 8.3$  Hz, 2H), 4.03 (s, 3H).

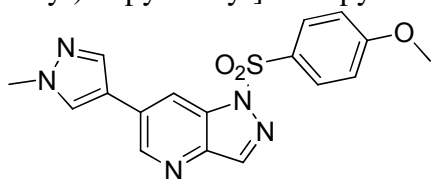
Example 16: Preparation of 1-(3-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3-trifluoromethylphenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(3-trifluoromethylbenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.87 (s, 1H), 8.47 (s, 1H), 8.41 (s, 1H), 8.31 (s, 1H), 8.22 (d,  $J = 8.2$  Hz, 1H), 7.95 (s, 1H), 7.93 – 7.83 (m, 2H), 7.68 (t,  $J = 8.0$  Hz, 1H), 4.03 (s, 3H).

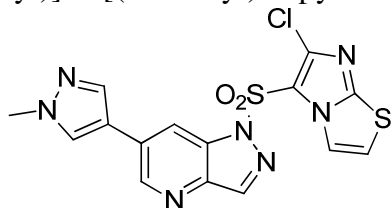
Example 17: Preparation of 1-(4-methoxybenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-methoxyphenylsulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(4-methoxybenzenesulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.84 (s, 1H), 8.49 (d,  $J = 1.0$  Hz, 1H), 8.36 (d,  $J = 0.6$  Hz, 1H), 7.96 (d,  $J = 2.1$  Hz, 1H), 7.94 (s, 2H), 7.85 (s, 1H), 6.94 (d,  $J = 9.1$  Hz, 2H), 4.03 (s, 3H), 3.83 (s, 3H).

Example 18: Preparation of 1-[(6-chloro-imidazo[2,1-b]thiazole)-5-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

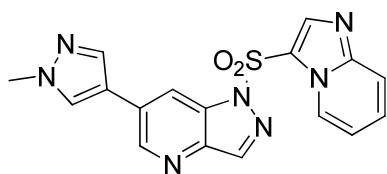


Except for (6-chloro-imidazo[2,1-b]thiazole)-5-sulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound

1-[(6-chloro-imidazo[2,1-b]thiazole)-5-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (d,  $J = 1.8$  Hz, 1H), 8.54 (s, 1H), 8.35 (s, 1H), 8.21 (d,  $J = 4.6$  Hz, 1H), 7.93 (s, 1H), 7.84 (s, 1H), 7.17 (d,  $J = 4.5$  Hz, 1H), 4.03 (s, 3H).

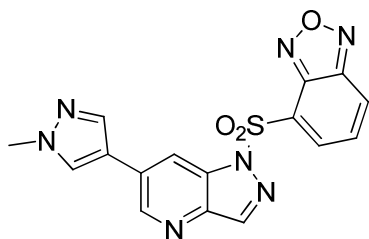
5                      Example                                              19:                                              Preparation                                              of  
1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyr  
idine



10                      Except for imidazo[1,2-a]pyridine-3-sulfonyl chloride was used instead of  
2-nitrophenylsulfonyl chloride, compound  
1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyr  
idine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.13 (d,  $J = 6.9$  Hz, 1H), 8.85 (d,  $J = 1.5$  Hz, 1H),  
8.46 (s, 1H), 8.32 (d,  $J = 3.4$  Hz, 2H), 7.94 (s, 1H), 7.86 (s, 1H), 7.74 (d,  $J = 9.2$  Hz, 1H),  
15                      7.61 – 7.46 (m, 1H), 7.17 (t,  $J = 6.9$  Hz, 1H), 4.03 (s, 3H).

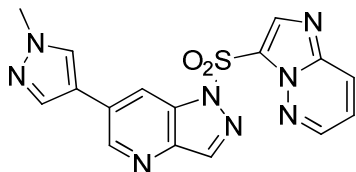
Example                                              20:                                              Preparation                                              of  
1-(benzo[1,2,5]oxadiazole-4-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyr  
idine



20                      Except for benzo[1,2,5]oxadiazole-4-sulfonyl chloride was used instead of  
2-nitrophenylsulfonyl chloride, compound  
1-(benzo[1,2,5]oxadiazole-4-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyr  
idine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.89 (d,  $J = 1.9$  Hz, 1H), 8.74 (dd,  $J = 1.9, 0.8$  Hz,  
25                      1H), 8.45 (dd,  $J = 6.9, 0.7$  Hz, 1H), 8.35 (d,  $J = 0.8$  Hz, 1H), 8.18 (dd,  $J = 9.0, 0.7$  Hz,  
1H), 8.00 (s, 1H), 7.93 (s, 1H), 7.65 (dd,  $J = 9.1, 6.9$  Hz, 1H), 4.05 (s, 3H).

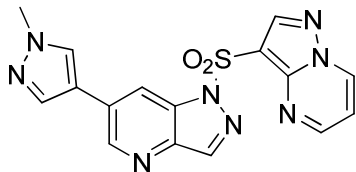
Example 21: Preparation of  
1-(imidazo[1,2-b]pyridazine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]p  
yridine



5 Except for imidazo[1,2-b]pyridazine-3-sulfonyl chloride was used instead of  
2-nitrophenylsulfonyl chloride, compound  
1-(imidazo[1,2-b]pyridazine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]p  
yridine was prepared by the same process as Example 3.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.87 (d, *J* = 1.9 Hz, 1H), 8.64 (dd, *J* = 1.9, 0.9 Hz,  
10 1H), 8.58 (s, 1H), 8.35 (d, *J* = 0.9 Hz, 1H), 8.30 (dd, *J* = 4.5, 1.6 Hz, 1H), 8.08 (dd, *J* =  
9.3, 1.6 Hz, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.89 (s, 1H), 7.26 – 7.23 (m, 1H), 4.04 (s, 3H).

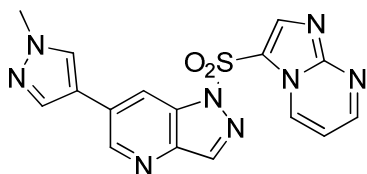
Example 22: Preparation of  
1-(pyrazolo[1,5-a]pyrimidine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]  
pyridine



15 Except for pyrazolo[1,5-a]pyrimidine-3-sulfonyl chloride was used instead of  
2-nitrophenylsulfonyl chloride, compound  
1-(pyrazolo[1,5-a]pyrimidine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]  
pyridine was prepared by the same process as Example 3.

20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.83 (d, *J* = 1.8 Hz, 1H), 8.76 (dd, *J* = 7.0, 1.7 Hz,  
1H), 8.71 (d, *J* = 4.1 Hz, 2H), 8.66 (s, 1H), 8.35 (s, 1H), 7.97 (s, 1H), 7.88 (s, 1H), 7.11  
(dd, *J* = 6.9, 4.3 Hz, 1H), 4.03 (s, 3H).

Example 23: Preparation of  
1-(imidazo[1,2-a]pyrimidine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]p  
yridine



Except for imidazo[1,2-a]pyrimidine-3-sulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound

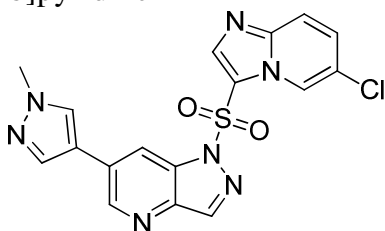
1-(imidazo[1,2-a]pyrimidine-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]p

5 yridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.82 (d,  $J = 1.8$  Hz, 1H), 8.74 (dd,  $J = 7.0, 1.8$  Hz, 1H), 8.71 (d,  $J = 4.2$  Hz, 2H), 8.63 (s, 1H), 8.37 (s, 1H), 7.95 (s, 1H), 7.83 (s, 1H), 7.12 (dd,  $J = 7.0, 4.3$  Hz, 1H), 4.04 (s, 3H).

Example 24: Preparation of

10 1-[(6-chloro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



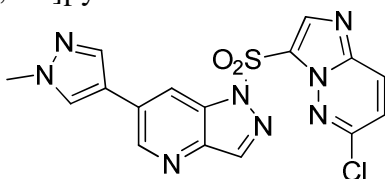
Except for (6-chloro-imidazo[1,2-a]pyridine)-3-sulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound

15 1-[(6-chloro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.20 (d,  $J = 1.1$  Hz, 1H), 8.87 (d,  $J = 1.9$  Hz, 1H), 8.44 (d,  $J = 1.0$  Hz, 1H), 8.37 (d,  $J = 0.8$  Hz, 1H), 8.28 (s, 1H), 7.95 (s, 1H), 7.86 (s, 1H), 7.68 (d,  $J = 8.8$  Hz, 1H), 7.50 (dd,  $J = 9.5, 2.0$  Hz, 1H), 4.04 (s, 3H).

20 Example 25: Preparation of

1-[(6-chloro-imidazo[1,2-b]pyridazine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

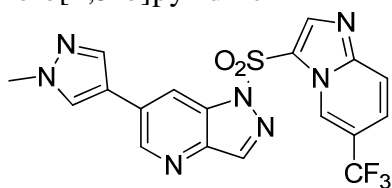


Except for (6-chloro-imidazo[1,2-b]pyridazine)-3-sulfonyl chloride was used instead

of 2-nitrophenylsulfonyl chloride, compound 1-[(6-chloro-imidazo[1,2-b]pyridazine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.89 (d, *J* = 1.9 Hz, 1H), 8.72 (d, *J* = 1.0 Hz, 1H), 8.54 (s, 1H), 8.37 (d, *J* = 0.6 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.92 (s, 1H), 7.21 (d, *J* = 9.5 Hz, 1H), 4.04 (s, 3H).

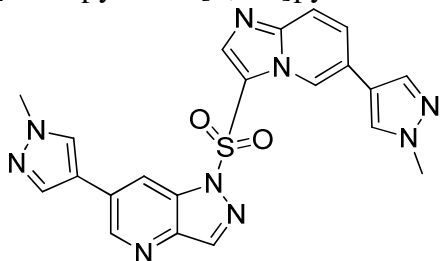
Example 26: Preparation of 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for (6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.53 (s, 1H), 8.87 (d, *J* = 1.9 Hz, 1H), 8.45 (s, 1H), 8.37 (d, *J* = 6.4 Hz, 2H), 7.95 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 1H), 4.04 (s, 3H).

Example 27: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

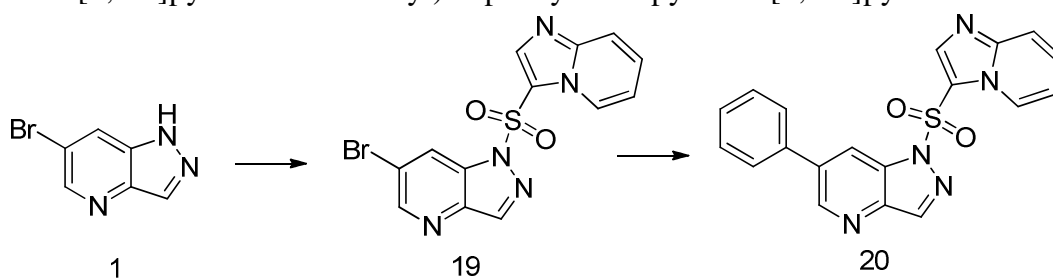


Into a microwave reaction tube were charged 120 mg Compound of Example 24, 64 mg 1-methyl-1H-pyrazolo-4-borate pinacol ester and 120 mg potassium carbonate, and 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 11.8 mg complex of

1,1'-bis(diphenylphosphino) ferrocene palladium (II) dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reacted at 90°C for 30 minutes, the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound (m=23 mg, yield: 17.3%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.17 (dd, *J* = 1.5, 0.9 Hz, 1H), 8.85 (d, *J* = 1.9 Hz, 1H), 8.46 (dd, *J* = 1.8, 0.8 Hz, 1H), 8.33 (d, *J* = 0.8 Hz, 1H), 8.28 (s, 1H), 7.95 (d, *J* = 0.4 Hz, 1H), 7.86 (s, 1H), 7.82 (d, *J* = 0.6 Hz, 1H), 7.74 (s, 1H), 7.72 (dd, *J* = 9.3, 0.8 Hz, 1H), 7.63 (dd, *J* = 9.3, 1.7 Hz, 1H), 4.04 (s, 3H), 4.00 (s, 3H).

Example 28: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-phenyl-1-H-pyrazolo[4,3-b]pyridine



Step 1: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-bromo-1-H-pyrazolo[4,3-b]pyridine

Forty six mg sodium hydride was dissolved in 15 ml anhydrous tetrahydrofuran, stirred for 5 minutes at room temperature. One hundred and sixty mg compound 1 was dissolved in 15 ml anhydrous tetrahydrofuran, then slowly and dropwisely added into sodium hydride solution in tetrahydrofuran, stirred overnight at room temperature after the addition was finished. One hundred and sixty seven mg imidazo[1,2-a]pyridine-3-sulfonyl chloride was dissolved in 15 ml anhydrous tetrahydrofuran, slowly and dropwisely added into the reactant liquid, stirred overnight at room temperature after the addition was finished, the reaction was completed. Tetrahydrofuran was removed by evaporation, and the remainder was dissolved in dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography

to obtain compound 19 (m=231 mg, yield: 79%).

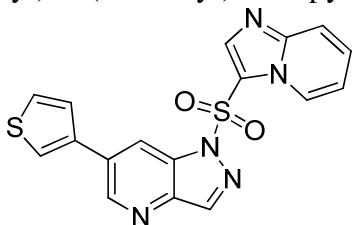
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.10 (d, *J* = 6.9 Hz, 1H), 8.74 (d, *J* = 1.9 Hz, 1H), 8.68 (dd, *J* = 1.9, 0.9 Hz, 1H), 8.34 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 9.1 Hz, 1H), 7.60 – 7.50 (m, 1H), 7.19 (dd, *J* = 7.5, 6.4 Hz, 1H).

Step 2: Preparation of  
1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-phenyl-1-H-pyrazolo[4,3-b]pyridine

Eighty mg 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-bromo-1-H-pyrazolo[4,3-b]pyridine, 31 mg phenylboronic acid and 88 mg potassium carbonate were charged into a microwave reaction tube, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 8.6 mg complex of 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reaction was conducted at a temperature of 120°C for 30 minutes, till the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound (m=54 mg, yield: 68%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.14 (dd, *J* = 5.8, 1.1 Hz, 1H), 8.95 (d, *J* = 1.9 Hz, 1H), 8.62 (dd, *J* = 1.9, 0.9 Hz, 1H), 8.39 (d, *J* = 0.8 Hz, 1H), 8.33 (s, 1H), 7.78 – 7.67 (m, 3H), 7.62 – 7.47 (m, 4H), 7.21 – 7.13 (m, 1H).

Example 29: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(3-thienyl)-1-H-pyrazolo[4,3-b]pyridine



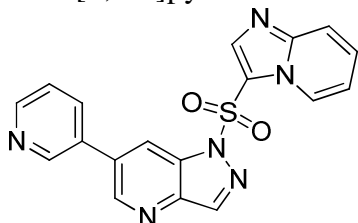
25 Except for 3-thiopheneboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(3-thienyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.13 (dt, *J* = 6.9, 1.2 Hz, 1H), 8.87 (d, *J* = 1.9 Hz, 1H),

8.48 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.35 (d,  $J = 0.9$  Hz, 1H), 8.33 (s, 1H), 7.99 – 7.94 (m, 1H), 7.75 (dt,  $J = 9.1, 1.1$  Hz, 1H), 7.64 – 7.58 (m, 1H), 7.54 (ddd,  $J = 9.0, 7.0, 1.3$  Hz, 1H), 7.18 (td,  $J = 7.0, 1.2$  Hz, 1H), 6.87 (dd,  $J = 1.9, 0.9$  Hz, 1H).

Example 30: Preparation of

5 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(3-pyridinyl)-1-H-pyrazolo[4,3-b]pyridine

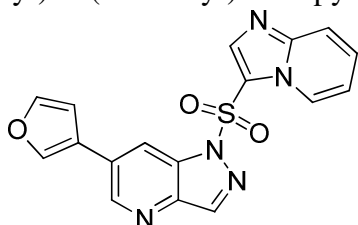


Except for 3-pyridineboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(3-pyridinyl)-1-H-pyrazolo [4,3-b]pyridine was prepared by the same process as Example 28.

10  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.15 (d,  $J = 6.9$  Hz, 1H), 9.03 – 8.91 (m, 2H), 8.77 (d,  $J = 3.9$  Hz, 1H), 8.64 (dd,  $J = 1.8, 0.8$  Hz, 1H), 8.43 (d,  $J = 0.7$  Hz, 1H), 8.34 (s, 1H), 8.06 – 7.97 (m, 1H), 7.76 (d,  $J = 9.0$  Hz, 1H), 7.60 – 7.46 (m, 2H), 7.20 (td,  $J = 7.0, 1.0$  Hz, 1H).

Example 31: Preparation of 1-(imidazo[1,2-a]pyridine-3-

15 sulfonyl)-6-(3-furanyl)-1-H-pyrazolo[4,3-b]pyridine

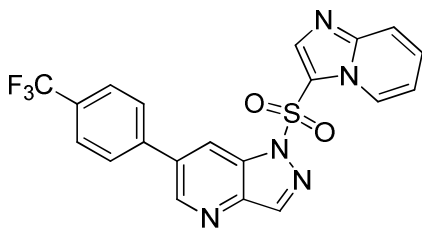


Except for 3-furanboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(3-furanyl)-1-H-pyrazolo [4,3-b]pyridine was prepared by the same process as Example 28.

20  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.13 (dt,  $J = 6.9, 1.2$  Hz, 1H), 8.98 (d,  $J = 1.9$  Hz, 1H), 8.60 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.36 (d,  $J = 0.9$  Hz, 1H), 8.33 (s, 1H), 7.78 – 7.69 (m, 2H), 7.58 – 7.49 (m, 3H), 7.17 (td,  $J = 7.0, 1.2$  Hz, 1H).

Example 32: Preparation of

25 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-trifluoromethylphenyl)-1-H-pyrazolo[4,3-b]pyridine



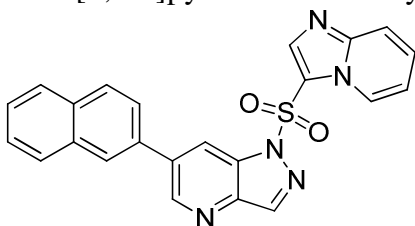
Except for 4-trifluoromethylphenylboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-trifluoromethylphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as

5 Example 28.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.15 (d,  $J = 6.9$  Hz, 1H), 8.95 (d,  $J = 1.8$  Hz, 1H), 8.64 (s, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 7.89 – 7.79 (m, 4H), 7.76 (d,  $J = 9.1$  Hz, 1H), 7.60 – 7.50 (m, 1H), 7.19 (t,  $J = 7.0$  Hz, 1H).

Example 33: Preparation of

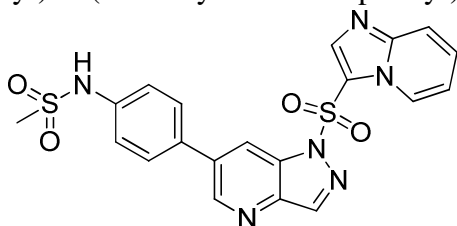
10 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(2-naphthyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 2-naphthylboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(2-naphthyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

15  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.15 (dt,  $J = 6.9, 1.2$  Hz, 1H), 9.08 (d,  $J = 1.9$  Hz, 1H), 8.74 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.42 (d,  $J = 0.9$  Hz, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.04 (d,  $J = 8.7$  Hz, 1H), 8.02 – 7.97 (m, 1H), 7.97 – 7.92 (m, 1H), 7.81 (dd,  $J = 8.5, 1.9$  Hz, 1H), 7.78 – 7.72 (m, 1H), 7.63 – 7.57 (m, 2H), 7.57 – 7.49 (m, 1H), 7.18 (td,  $J = 7.0, 1.1$  Hz, 1H).

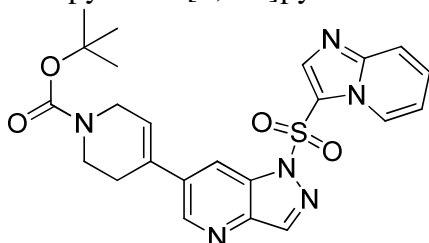
20 Example 34: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-methylsulfamidophenyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 4-methylsulfamidophenylboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-methylsulfamidophenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

5  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  10.08 (s, 1H), 9.06 (d,  $J$  = 1.9 Hz, 1H), 8.98 (d,  $J$  = 6.8 Hz, 1H), 8.81 (d,  $J$  = 0.8 Hz, 1H), 8.71 (s, 1H), 8.60 (d,  $J$  = 1.1 Hz, 1H), 7.91 (d,  $J$  = 8.7 Hz, 2H), 7.86 (d,  $J$  = 9.0 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.41 (dd,  $J$  = 11.3, 4.5 Hz, 3H).

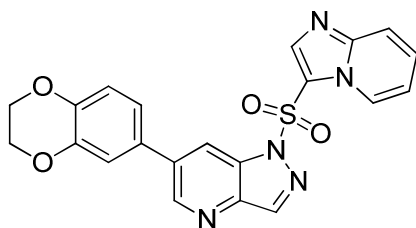
Example 35: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[(1-t-butoxycarbonyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine



Except for (1-t-butoxycarbonyl)-4-1,2,3,6-tetrahydropyridineborate pinacol ester was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[(1-t-butoxycarbonyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

15  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.12 (d,  $J$  = 6.9 Hz, 1H), 8.77 (d,  $J$  = 1.7 Hz, 1H), 8.33 (t,  $J$  = 8.0 Hz, 3H), 7.74 (d,  $J$  = 9.0 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.17 (t,  $J$  = 6.9 Hz, 1H), 6.40 – 6.21 (m, 1H), 4.25 – 4.13 (m, 2H), 3.74 (t,  $J$  = 5.6 Hz, 2H), 2.72 – 2.56 (m, 20 2H), 1.52 (s, 9H).

Example 36: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[6-(1,4-benzodioxanyl)]-1-H-pyrazolo[4,3-b]pyridine

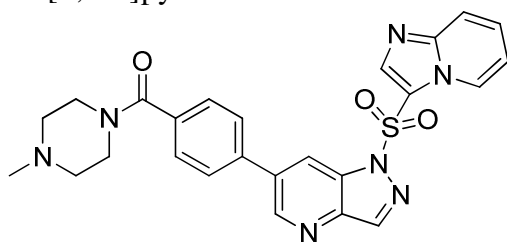


25 Except for 6-(1,4-benzodioxanyl)boronic acid was used instead of phenylboronic

acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[6-(1,4-benzodioxanyl)]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.12 (d, *J* = 6.9 Hz, 1H), 8.89 (d, *J* = 1.9 Hz, 1H), 8.53 (dd, *J* = 1.9, 0.9 Hz, 1H), 8.36 (d, *J* = 0.9 Hz, 1H), 8.32 (s, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.25 – 7.12 (m, 3H), 7.04 (d, *J* = 8.3 Hz, 1H), 4.36 (s, 4H).

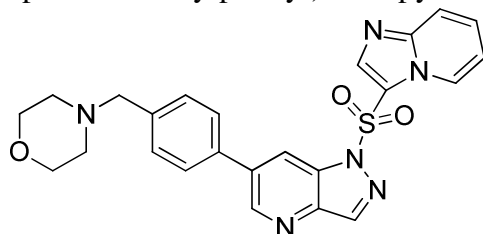
Example 37: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-(4-methylpiperazine-1-carbonyl)phenylboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.14 (d, *J* = 6.9 Hz, 1H), 8.94 (d, *J* = 1.9 Hz, 1H), 8.61 (d, *J* = 1.1 Hz, 1H), 8.41 (d, *J* = 0.8 Hz, 1H), 8.33 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 3H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.51 (m, 1H), 7.19 (t, *J* = 6.4 Hz, 1H), 3.95 – 3.80 (m, 2H), 3.63 – 3.48 (m, 2H), 2.66 – 2.51 (m, 2H), 2.51 – 2.39 (m, 2H), 2.38 (s, 3H).

Example 38: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-morpholinomethylphenyl)-1-H-pyrazolo[4,3-b]pyridine

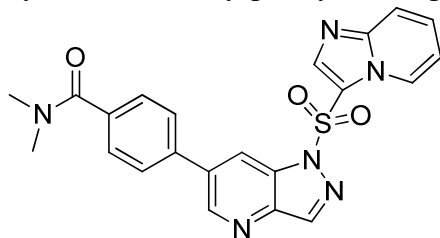


Except for 4-morpholinomethylphenylboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-morpholinomethylphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.



7.19 (td,  $J = 6.9, 1.0$  Hz, 1H), 2.70 (s, 3H).

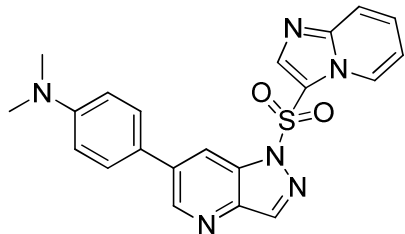
Example 41: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-dimethylaminocarbonylphenyl)-1-H-pyrazolo[4,3-b]pyridine



5 Except for 4-dimethylaminocarbonylphenylboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-dimethylaminocarbonylphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.14 (d,  $J = 6.9$  Hz, 1H), 8.95 (d,  $J = 1.9$  Hz, 1H),  
10 8.62 (d,  $J = 1.8$  Hz, 1H), 8.41 (s, 1H), 8.34 (s, 1H), 7.75 (dd,  $J = 8.5, 2.0$  Hz, 3H), 7.63 (d,  $J = 8.1$  Hz, 2H), 7.59 – 7.50 (m, 1H), 7.19 (t,  $J = 6.6$  Hz, 1H), 3.18 (s, 3H), 3.08 (s, 3H).

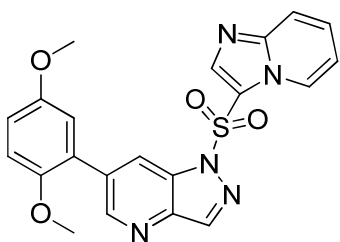
Example 42: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-dimethylaminophenyl)-1-H-pyrazolo[4,3-b]pyridine



15 Except for 4-dimethylaminophenylboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(4-dimethylaminophenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.11 (d,  $J = 6.9$  Hz, 1H), 8.85 (d,  $J = 1.8$  Hz, 1H),  
20 8.61 (dd,  $J = 1.8, 0.9$  Hz, 1H), 8.38 (d,  $J = 0.9$  Hz, 1H), 8.32 (s, 1H), 7.77 – 7.70 (m, 2H), 7.65 – 7.59 (m, 1H), 7.56 – 7.47 (m, 2H), 7.16 (td,  $J = 6.9, 1.2$  Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H).

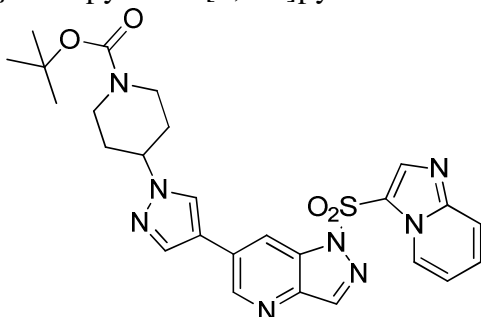
Example 43: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(2,5-dimethoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 2,5-dimethoxyphenylboronic acid was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-(2,5-dimethoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.11 (d,  $J = 6.9$  Hz, 1H), 8.85 (d,  $J = 1.8$  Hz, 1H), 8.61 (d,  $J = 0.9$  Hz, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 7.74 (d,  $J = 9.0$  Hz, 1H), 7.57 – 7.46 (m, 1H), 7.20 – 7.10 (m, 1H), 7.02 – 6.89 (m, 3H), 3.86 (s, 3H), 3.82 (s, 3H).

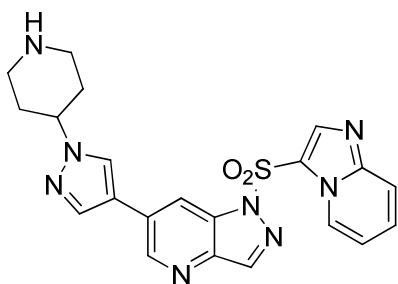
Example 44: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Except for {{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazoloborate pinacol ester was used instead of phenylboronic acid, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.13 (d,  $J = 7.0$  Hz, 1H), 8.86 (d,  $J = 1.9$  Hz, 1H), 8.45 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.33 (d,  $J = 0.9$  Hz, 2H), 7.96 (d,  $J = 0.7$  Hz, 1H), 7.90 (s, 1H), 7.75 (d,  $J = 9.1$  Hz, 1H), 7.58 – 7.49 (m, 1H), 7.17 (dd,  $J = 7.4, 6.5$  Hz, 1H), 4.44 – 4.33 (m, 3H), 3.04 – 2.83 (m, 2H), 2.23 (d,  $J = 10.9$  Hz, 2H), 2.10 – 1.93 (m, 2H), 1.50 (s, 9H).

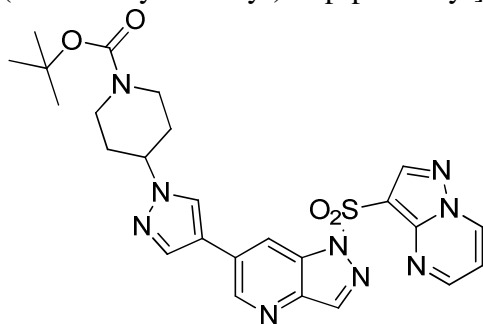
Example 45: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-(4-piperidinyl)}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Fifty mg compound of Example 44 was dissolved in 5 ml dioxane saturated with hydrochloric acid, stirred for 30 minutes at room temperature. The reaction was completed, the pH was adjusted to 8~9 using saturated sodium carbonate solution, and diluted by adding 20 ml dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound (m=37 mg, yield: 91%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.14 (d,  $J = 7.0$  Hz, 1H), 8.87 (s, 1H), 8.51 (s, 1H), 8.35 (s, 1H), 8.34 (s, 1H), 8.16 (s, 1H), 7.99 (s, 1H), 7.75 (d,  $J = 9.0$  Hz, 1H), 7.60 – 7.54 (m, 1H), 7.21 (t,  $J = 7.2$  Hz, 1H), 3.75 – 3.58 (m, 3H), 3.33 – 3.18 (m, 2H), 2.50 – 2.45 (m, 2H), 2.08 – 2.03 (m, 2H).

Example 46: Preparation of 1-(pyrazolo[1,5-a]pyrimidine-3-sulfonyl)-6-{{1-[(1-t-butoxycarbonyl)-4-piperidiny]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine

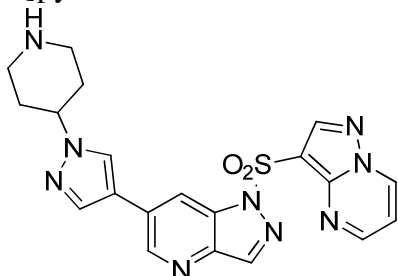


Except for {{1-[(1-t-butoxycarbonyl)-4-piperidiny]}-4-pyrazoloborate pinacol ester was used instead of 1-methyl-1H-pyrazolo-4-boronic acid pinacol ester, compound 1-(pyrazolo[1,5-a]pyrimidine-3-sulfonyl)-6-{{1-[(1-t-butoxycarbonyl)-4-piperidiny]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 22.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.84 (d,  $J = 1.9$  Hz, 1H), 8.76 (dd,  $J = 7.0, 1.6$  Hz, 1H), 8.72 – 8.68 (m, 2H), 8.67 (s, 1H), 8.34 (s, 1H), 7.99 (s, 1H), 7.92 (s, 1H), 7.11 (dd,  $J = 7.0, 4.2$  Hz, 1H), 4.44 – 4.23 (m, 3H), 3.03 – 2.86 (m, 2H), 2.28 – 2.18 (m, 2H), 2.12 –

1.93 (m, 2H), 1.50 (s, 9H).

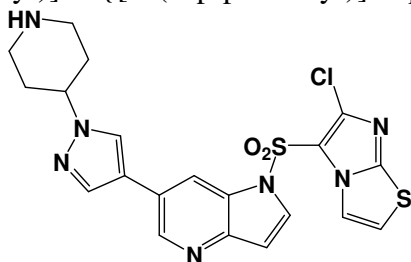
Example 47: Preparation of 1-(imidazo[1,2-a]pyrimidine-3-sulfonyl)-6-[[1-(4-piperidinyl)]-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Fifty mg compound of Example 46 was dissolved in 5 ml dioxane saturated with hydrochloric acid, stirred for 30 minutes at room temperature. The reaction was completed, and filtered to obtain filter cake, which was washed three times by ether immersion, dried at vacuum to produce the target compound (m=37 mg, yield: 91%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.84 (d, *J* = 1.9 Hz, 1H), 8.77 (dd, *J* = 7.0, 1.6 Hz, 1H), 8.72 – 8.64 (m, 2H), 8.65 (s, 1H), 8.31 (s, 1H), 7.79 (s, 1H), 7.91 (s, 1H), 7.01 (dd, *J* = 7.0, 4.2 Hz, 1H), 4.44 – 4.35 (m, 3H), 3.23 – 2.96 (m, 2H), 2.33 – 2.28 (m, 2H), 2.02 – 1.93 (m, 2H).

Example 48: Preparation of 1-[(6-chloro-imidazo[2,1-b]thiazole)-5-sulfonyl]-6-[[1-(4-piperidinyl)]-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

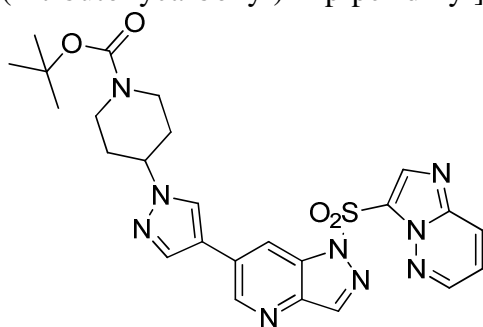


Except for {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazoloborate pinacol ester was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(6-chloro-imidazo[2,1-b]thiazole)-5-sulfonyl]-6-[[1-(4-piperidinyl)]-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 18. Eighty seven mg 1-[(6-chloro-imidazo[2,1-b]thiazole)-5-sulfonyl]-6-[[1-(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was dissolved in 5 ml dioxane saturated

with hydrochloric acid, stirred for 30 minutes at room temperature. The reaction was completed, and filtered to obtain filter cake, which was washed three times by ether immersion, dried at vacuum to produce the target compound (m=65 mg, yield: 90%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.71 (d, *J* = 1.9 Hz, 1H), 8.21 (dd, *J* = 1.9, 0.7 Hz, 1H), 8.12 (d, *J* = 4.5 Hz, 1H), 7.84 (d, *J* = 3.8 Hz, 1H), 7.82 (s, 1H), 7.81 (s, 1H), 7.53 (d, *J* = 4.5 Hz, 1H), 7.50 (t, *J* = 2.0 Hz, 1H), 6.87 (dd, *J* = 3.8, 0.7 Hz, 1H), 4.67 – 4.52 (m, 1H), 3.71 – 3.57 (m, 2H), 2.70 – 2.53 (m, 2H), 2.53 – 2.39 (m, 4H).

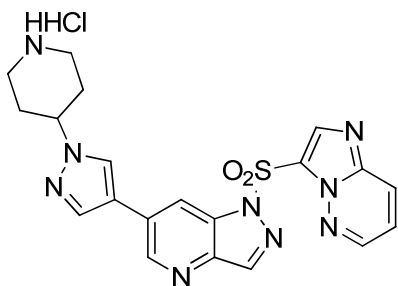
Example 49: Preparation of 1-(imidazo[1,2-b]pyridazine-3-sulfonyl)-6-{{1-[(1-*t*-butoxycarbonyl)-4-piperidiny]]-4-pyrazolyl}-1-*H*-pyrazolo[4,3-*b*]pyridine



Except for {1-[(1-*t*-butoxycarbonyl)-4-piperidiny]]-4-pyrazoloborate pinacol ester was used instead of 1-methyl-1*H*-pyrazolo-4-borate pinacol ester, compound 1-(imidazo[1,2-*b*]pyridazine-3-sulfonyl)-6-{{1-[(1-*t*-butoxycarbonyl)-4-piperidiny]]-4-pyrazolyl}-1-*H*-pyrazolo[4,3-*b*]pyridine was prepared by the same process as Example 21.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.88 (d, *J* = 1.9 Hz, 1H), 8.64 (dd, *J* = 1.9, 0.8 Hz, 1H), 8.58 (s, 1H), 8.35 (d, *J* = 0.8 Hz, 1H), 8.31 (dd, *J* = 4.5, 1.6 Hz, 1H), 8.08 (dd, *J* = 9.3, 1.6 Hz, 1H), 8.00 (d, *J* = 0.6 Hz, 1H), 7.94 (s, 1H), 7.26 (dd, *J* = 9.3, 4.5 Hz, 1H), 4.46 – 4.23 (m, 3H), 3.04 – 2.85 (m, 2H), 2.28 – 2.19 (m, 2H), 2.10 – 1.95 (m, 2H), 1.50 (s, 9H).

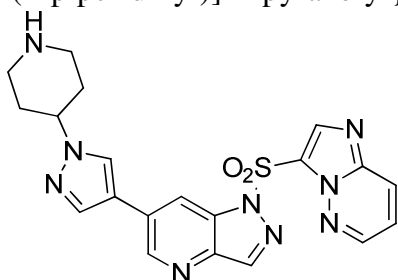
Example 50: Preparation of 1-(imidazo[1,2-*b*]pyridazine-3-sulfonyl)-6-[[1-(4-piperidiny)]-4-pyrazolyl]-4-pyrazolyl-1-*H*-pyrazolo[4,3-*b*]pyridine chloride



Fifty mg compound of Example 49 was dissolved in 5 ml dioxane saturated with hydrochloric acid, stirred for 30 minutes at room temperature. The reaction was completed, and filtered to obtain filter cake, which was washed three times by ether immersion, dried  
5 at vacuum to obtain the target compound (m=35 mg, yield: 89%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (d,  $J = 1.8$  Hz, 1H), 8.65 (s, 1H), 8.59 (s, 1H), 8.36 (s, 2H), 8.08 (dd,  $J = 9.3, 1.4$  Hz, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.30 – 7.25 (m, 1H), 4.67 – 4.54 (m, 1H), 3.77 – 3.66 (m, 2H), 3.32 – 3.20 (m, 2H), 2.70 – 2.51 (m, 4H).

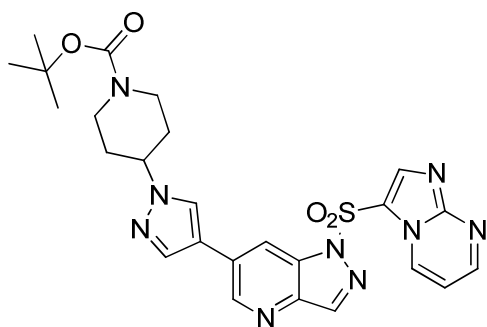
Example 51: Preparation of 1-(imidazo[1,2-b]pyridazine-3-sulfonyl)-  
10 6-[[1-(4-piperidinyl)]-4-pyrazolyl]-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Fifty mg compound of Example 50 was dissolved in 10 ml saturated sodium bicarbonate solution, stirred for 5 minutes. The aqueous solution was extracted three times with dichloromethane, evaporated to dry, the organic layer was dried over anhydrous  
15 sodium sulfate then concentrated, dried at vacuum to obtain the target compound (m=45 mg, yield: 98%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (d,  $J = 1.8$  Hz, 1H), 8.65 (s, 1H), 8.59 (s, 1H), 8.36 (s, 2H), 8.08 (dd,  $J = 9.3, 1.4$  Hz, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.30 – 7.25 (m, 1H), 4.67 – 4.54 (m, 1H), 3.77 – 3.66 (m, 2H), 3.32 – 3.20 (m, 2H), 2.70 – 2.51 (m, 4H).

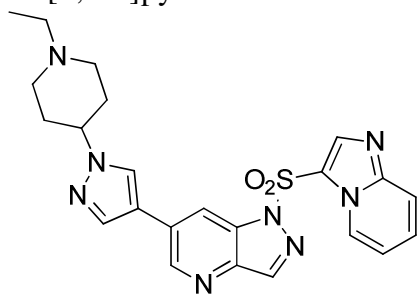
20 Example 52: Preparation of 1-(imidazo[1,2-a]pyrimidine-3-sulfonyl)-6-[[1-(1-t-butoxycarbonyl)-4-piperidinyl]]-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazoloborate pinacol ester was used instead of 1-methyl-1H-pyrazolo-4-boronic acid pinacol ester, compound 1-(imidazo[1,2-a]pyrimidine-3-sulfonyl)-6-{ {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 23.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.87 (d, *J* = 1.9 Hz, 1H), 8.68 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.65 (dd, *J* = 1.8, 0.8 Hz, 1H), 8.54 (dd, *J* = 6.9, 2.0 Hz, 1H), 8.37 (s, 1H), 8.37 (d, *J* = 0.8 Hz, 1H), 7.97 (s, 1H), 7.94 (s, 1H), 7.06 (dd, *J* = 6.9, 4.0 Hz, 1H), 4.44 – 4.28 (m, 3H), 3.02 – 2.83 (m, 2H), 2.27 – 2.16 (m, 2H), 2.10 – 1.94 (m, 2H).

Example 53: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{ {1-[(1-ethyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine

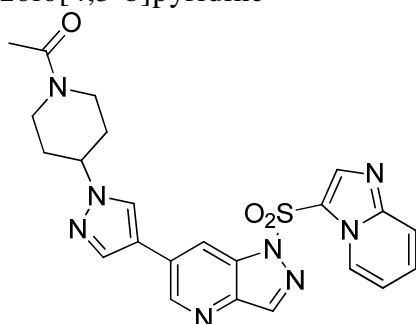


Fifty milligrams compound of Example 45 was dissolved in 5 ml methanol, then 12.5 μl acetaldehyde, 319 μl acetic acid and 17.5 mg sodium cyanoborohydride were sequentially added, stirred at room temperature for 5 hours, the reaction was completed. The reactant liquid was diluted with 20 ml dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound (m=47 mg, yield: 88%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.02 (d, *J* = 7.1 Hz, 1H), 8.78 (s, 1H), 8.42 (s, 1H),

8.29 – 8.22 (m, 3H), 7.87 (s, 1H), 7.63 (dt,  $J = 9.0, 1.2$  Hz, 1H), 7.48 (t,  $J = 8.0$  Hz, 1H), 7.13 (td,  $J = 7.0, 1.2$  Hz, 1H), 4.82 (d,  $J = 13.6$  Hz, 1H), 4.52 - 4.40 (m, 1H), 4.03 (d,  $J = 13.6$  Hz, 1H), 3.36 - 3.25 (m, 1H), 2.81 (dd,  $J = 18.6, 7.3$  Hz, 1H), 2.29 (dd,  $J = 24.4, 12.2$  Hz, 2H), 2.18 (m, 2H), 2.13 - 1.96 (m, 2H), 1.35 (t,  $J = 6.6$  Hz, 3H).

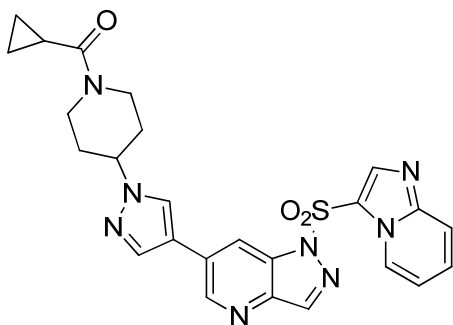
5                      Example                                      54:                                      Preparation                                      of  
1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-acetyl)-4-piperidiny]}-4-pyrazolyl}-1-H  
-pyrazolo[4,3-b]pyridine



10                      Fifty milligrams compound of Example 45 and 46.6  $\mu$ l triethylamine were dissolved  
in 10 ml dichloromethane, then 8.7  $\mu$ l acetyl chloride was added dropwise, stirred for 30  
minutes at room temperature, the reaction was completed. The reactant liquid was washed  
three times with water, the organic layer was dried over anhydrous sodium sulfate then  
concentrated, and isolated by flash preparative chromatography to obtain the target  
compound (m=48 mg, yield: 88%).

15                       $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.13 (d,  $J = 6.9$  Hz, 1H), 8.85 (d,  $J = 1.8$  Hz, 1H),  
8.46 (d,  $J = 1.0$  Hz, 1H), 8.32 (d,  $J = 4.7$  Hz, 2H), 7.97 (s, 1H), 7.91 (s, 1H), 7.74 (d,  $J =$   
9.0 Hz, 1H), 7.58 - 7.48 (m, 1H), 7.18 (t,  $J = 6.9$  Hz, 1H), 4.82 (d,  $J = 13.6$  Hz, 1H), 4.52 -  
4.40 (m, 1H), 4.03 (d,  $J = 13.6$  Hz, 1H), 3.36 - 3.25 (m, 1H), 2.81 (dd,  $J = 18.6, 7.3$  Hz,  
1H), 2.29 (dd,  $J = 24.4, 12.2$  Hz, 2H), 2.18 (s, 3H), 2.13 - 1.96 (m, 2H).

20                      Example                                      55:                                      Preparation                                      of  
1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopropylcarbonyl)-4-piperidiny]}-4-p  
yrazolyl}-1-H-pyrazolo[4,3-b]pyridine

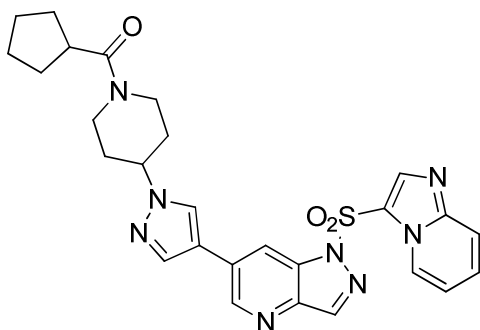


Except for cyclopropylcarbonyl chloride was used instead of acetyl chloride, compound

1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopropylcarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 54.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.14 (d, *J* = 6.8 Hz, 1H), 8.86 (s, 1H), 8.46 (s, 1H), 8.34 (s, 2H), 7.97 (s, 1H), 7.93 (s, 1H), 7.77 (d, *J* = 9.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.20 (t, *J* = 6.9 Hz, 1H), 4.88 – 4.66 (m, 1H), 4.57 – 4.35 (m, 2H), 3.44 – 3.26 (m, 1H), 2.95 – 2.75 (m, 1H), 2.42 – 2.20 (m, 2H), 2.20 – 1.95 (m, 2H), 1.87 – 1.75 (m, 1H), 1.11 – 0.96 (m, 2H), 0.87 – 0.74 (m, 2H).

Example 56: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopentylcarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



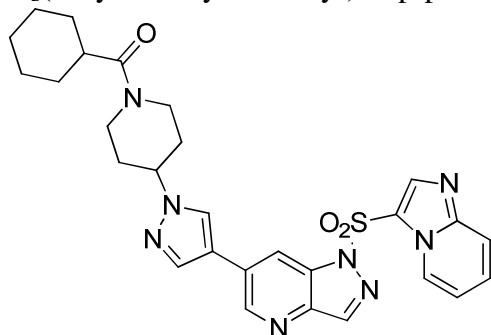
Except for cyclopentylcarbonyl chloride was used instead of acetyl chloride, compound

1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopentylcarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 54.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.16 – 9.08 (m, 1H), 8.85 (d, *J* = 0.8 Hz, 1H), 8.45 (s, 1H), 8.32 (d, *J* = 4.4 Hz, 2H), 7.97 (s, 1H), 7.91 (s, 1H), 7.80 – 7.67 (m, 1H), 7.54 (dd, *J* = 8.5, 7.6 Hz, 1H), 7.18 (t, *J* = 7.0 Hz, 1H), 4.85 (d, *J* = 13.5 Hz, 1H), 4.56 – 4.38 (m, 1H), 4.14 (d, *J* = 13.3 Hz, 1H), 3.25 (t, *J* = 12.9 Hz, 1H), 2.78 (t, *J* = 12.4 Hz, 1H), 2.64 – 2.46

(m, 1H), 2.36 – 2.24 (m, 2H), 2.07 – 1.96 (m, 2H), 1.81 – 1.72 (m, 3H), 1.61 – 1.50 (m, 2H), 1.32 – 1.24 (m, 3H).

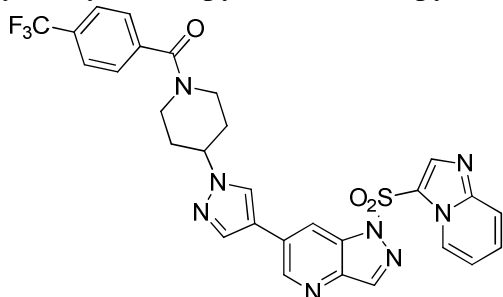
Example 57: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclohexylcarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Except for cyclohexylcarbonyl chloride was used instead of acetyl chloride, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclohexylcarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 54.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.13 (d, *J* = 6.9 Hz, 1H), 8.85 (d, *J* = 1.8 Hz, 1H), 8.46 (d, *J* = 1.5 Hz, 1H), 8.32 (d, *J* = 4.1 Hz, 2H), 7.97 (s, 1H), 7.91 (s, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.18 (t, *J* = 6.5 Hz, 1H), 4.85 (d, *J* = 13.7 Hz, 1H), 4.54 – 4.41 (m, 1H), 4.20 (d, *J* = 14.4 Hz, 1H), 3.26 (t, *J* = 12.0 Hz, 1H), 2.96 (p, *J* = 8.0 Hz, 1H), 2.81 (t, *J* = 11.8 Hz, 1H), 2.38 – 2.21 (m, 2H), 2.08 – 1.98 (m, 2H), 1.95 – 1.81 (m, 5H), 1.79 – 1.73 (m, 2H), 1.69 – 1.51 (m, 3H).

Example 58: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-p-trifluoromethylbenzoyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine

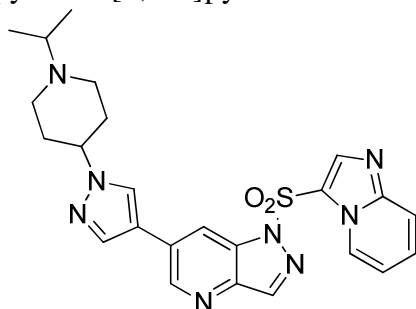


Except for p-trifluoromethyl benzoyl chloride was used instead of acetyl chloride, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-p-trifluoromethylbenzoyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was

prepared by the same process as Example 54.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.16 (d, *J* = 6.7 Hz, 1H), 8.87 (s, 1H), 8.47 (s, 1H), 8.34 (s, 2H), 7.98 (s, 1H), 7.95 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 3H), 7.22 (t, *J* = 6.8 Hz, 1H), 5.01 – 4.82 (m, 1H), 4.59 – 4.44 (m, 1H), 4.01 – 3.81 (m, 1H), 3.35 – 3.18 (m, 1H), 3.17 – 2.99 (m, 1H), 2.44 – 2.01 (m, 4H).

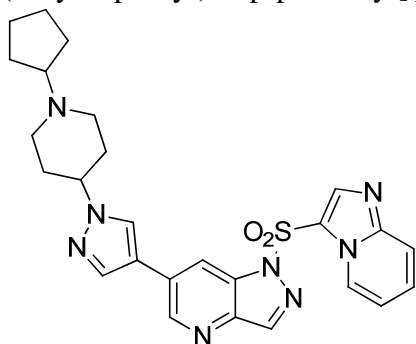
Example 59: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-isopropyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Except for acetone was used instead of acetaldehyde, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-isopropyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 53.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.12 (dt, *J* = 6.9, 1.1 Hz, 1H), 8.85 (d, *J* = 1.9 Hz, 1H), 8.46 (dd, *J* = 1.9, 0.9 Hz, 1H), 8.35 – 8.31 (m, 2H), 8.00 (s, 1H), 7.94 (d, *J* = 0.6 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.58 – 7.49 (m, 1H), 7.18 (td, *J* = 7.0, 1.2 Hz, 1H), 4.57 – 4.44 (m, 1H), 3.53 – 3.41 (m, 2H), 3.38 – 3.23 (m, 1H), 2.99 – 2.84 (m, 2H), 2.70 – 2.53 (m, 2H), 2.53 – 2.37 (m, 2H), 1.35 (d, *J* = 6.6 Hz, 6H).

Example 60: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopentyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine

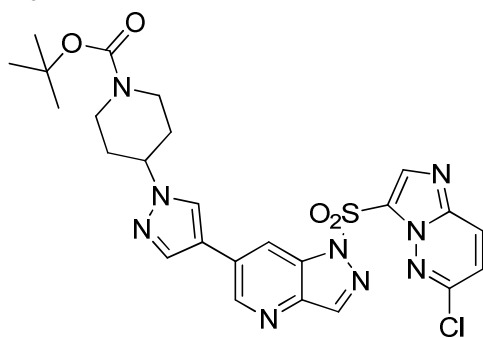


Except for cyclopentanone was used instead of acetaldehyde, compound 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-{{1-[(1-cyclopentyl)-4-piperidinyl]}-4-pyrazolyl}

}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 53.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.13 (dd, *J* = 6.9, 1.1 Hz, 1H), 8.88 – 8.82 (m, 1H), 8.46 (s, 1H), 8.33 (s, 2H), 7.96 (d, *J* = 15.3 Hz, 2H), 7.75 (dd, *J* = 9.1, 1.0 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.18 (t, *J* = 7.0 Hz, 1H), 4.52 – 4.37 (m, 1H), 3.52 – 3.39 (m, 2H), 3.08 – 2.90 (m, 1H), 2.86 – 2.62 (m, 2H), 2.59 – 2.32 (m, 4H), 2.05 – 1.94 (m, 2H), 1.90 – 1.72 (m, 4H), 1.70 – 1.53 (m, 2H).

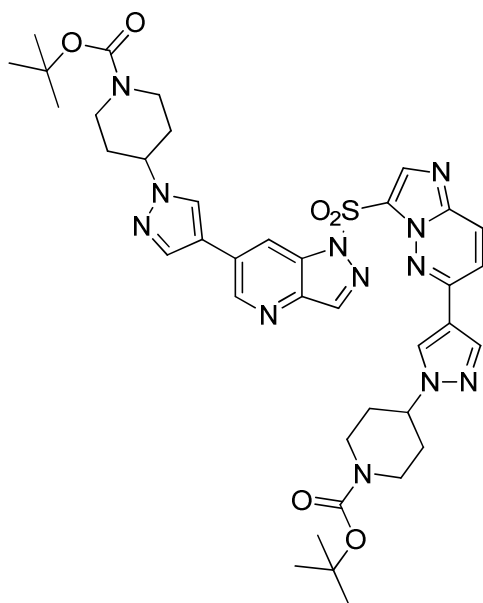
Example 61: Preparation of 1-[(6-chloro-imidazo[1,2-b]pyridazine)-3-sulfonyl]-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Except for {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazoloborate pinacol ester was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(6-chloro-imidazo[1,2-b]pyridazine)-3-sulfonyl]-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 25.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.89 (d, *J* = 1.8 Hz, 1H), 8.75 – 8.69 (m, 1H), 8.54 (s, 1H), 8.37 (d, *J* = 0.6 Hz, 1H), 8.00 (dd, *J* = 17.0, 7.4 Hz, 3H), 7.22 (d, *J* = 9.5 Hz, 1H), 4.44 – 4.24 (m, 3H), 3.03 – 2.86 (m, 2H), 2.31 – 2.17 (m, 2H), 2.01 (qd, *J* = 12.4, 4.4 Hz, 2H), 1.50 (s, 9H).

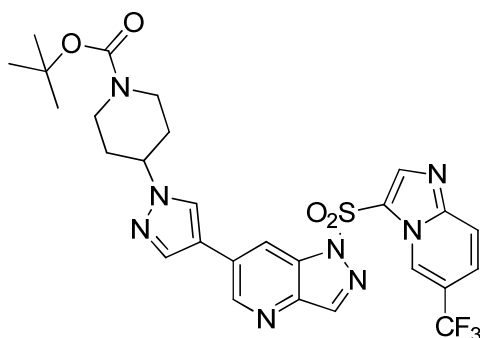
Example 62: Preparation of 1-[(6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-imidazo[1,2-b]pyridazine)-3-sulfonyl]-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Into a microwave reaction tube were charged 141 mg compound of Example 61, 100 mg {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4- pyrazoloborate pinacol ester and 100 mg potassium carbonate, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 9.8 mg complex of 1,1'-bis(diphenylphosphino) ferrocene palladium (II) dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reacted at 90 °C for 10 minutes, the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound (m=154 mg, yield: 80%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.94 (d, *J* = 1.8 Hz, 1H), 8.68 (d, *J* = 1.0 Hz, 1H), 8.55 (s, 1H), 8.35 (d, *J* = 0.7 Hz, 1H), 8.02 (dd, *J* = 6.8, 5.2 Hz, 3H), 7.57 (s, 1H), 7.40 (d, *J* = 9.6 Hz, 1H), 7.22 (s, 1H), 4.47 – 4.11 (m, 5H), 4.04 – 3.87 (m, 1H), 3.02 – 2.86 (m, 2H), 2.84 – 2.66 (m, 2H), 2.22 (d, *J* = 10.3 Hz, 2H), 2.03 (qd, *J* = 12.3, 4.4 Hz, 2H), 1.92 – 1.73 (m, 4H), 1.50 (d, *J* = 4.5 Hz, 18H).

Example 63: Preparation of 1-[(6-(trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl)]-6-{ {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine

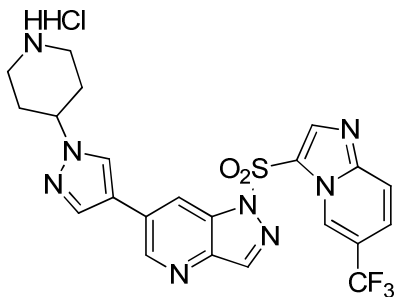


Except for {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazoloborate pinacol ester was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-

5 { {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl }-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 26.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.53 (dd, *J* = 1.7, 1.1 Hz, 1H), 8.87 (d, *J* = 1.9 Hz, 1H), 8.45 (dd, *J* = 1.9, 0.9 Hz, 1H), 8.37 (s, 1H), 8.36 (d, *J* = 0.9 Hz, 1H), 7.97 (d, *J* = 0.7 Hz, 1H), 7.91 (d, *J* = 0.6 Hz, 1H), 7.86 (d, *J* = 9.5 Hz, 1H), 7.68 (dd, *J* = 9.5, 1.8 Hz, 1H),  
10 4.46 – 4.25 (m, 3H), 3.03 – 2.86 (m, 2H), 2.29 – 2.18 (m, 2H), 2.02 (tt, *J* = 12.4, 6.2 Hz, 2H), 1.50 (s, 9H).

Example 64: Preparation of 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{[1-(4-piperidinyl)]-4-pyrazolyl}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine chloride

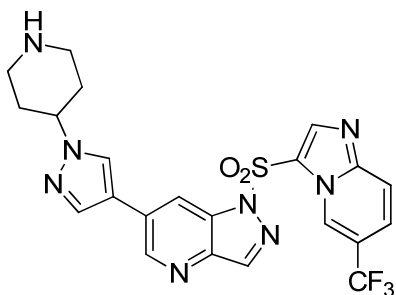


15

Fifty milligrams compound of Example 63 was dissolved in 5 ml dioxane saturated with hydrochloric acid, stirred for 30 minutes at room temperature. The reaction was completed, and filtered to obtain filter cake, which was washed three times by ether immersion, dried at vacuum to obtain the target compound (m=37 mg, yield: 83%).

20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.54 (s, 1H), 8.88 (s, 1H), 8.46 (s, 1H), 8.42 (s, 1H), 8.36 (s, 1H), 8.04 (s, 1H), 7.96 (s, 1H), 7.86 (d, *J* = 9.4 Hz, 1H), 7.68 (d, *J* = 9.5 Hz, 1H), 4.69 – 4.53 (m, 1H), 3.83 – 3.63 (m, 2H), 3.38 – 3.19 (m, 2H), 2.75 – 2.47 (m, 4H).

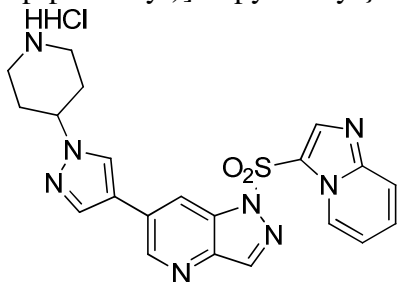
Example 65: Preparation of 1-[(6-(trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl)]-6-[[1-(4-piperidinyl)]-4-pyrazolyl]-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Fifty milligrams compound of Example 64 was added into 10 ml saturated sodium bicarbonate solution, stirred for 5 minutes. The aqueous solution was extracted three times with dichloromethane, evaporated to dry, the organic layer was dried over anhydrous sodium sulfate then concentrated, dried at vacuum to obtain the target compound (m=42 mg, yield: 97%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.54 (s, 1H), 8.88 (s, 1H), 8.46 (s, 1H), 8.42 (s, 1H), 8.36 (s, 1H), 8.04 (s, 1H), 7.96 (s, 1H), 7.86 (d,  $J = 9.4$  Hz, 1H), 7.68 (d,  $J = 9.5$  Hz, 1H), 4.69 – 4.53 (m, 1H), 3.83 – 3.63 (m, 2H), 3.38 – 3.19 (m, 2H), 2.75 – 2.47 (m, 4H).

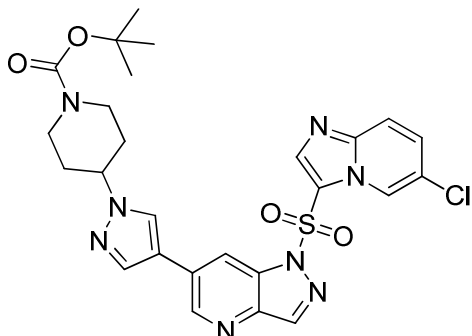
Example 66: Preparation of 1-(imidazo[1,2-a]pyridine-3-sulfonyl)-6-[[1-(4-piperidinyl)]-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine chloride



Fifty milligrams compound of Example 44 was dissolved in 5 ml dioxane saturated with hydrochloric acid, stirred for 30 minutes at room temperature. The reaction was completed, and filtered to obtain filter cake, which was washed three times by ether immersion, vacuum dried to obtain the target compound (m=36 mg, yield: 86%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.14 (d,  $J = 7.0$  Hz, 1H), 8.87 (s, 1H), 8.51 (s, 1H), 8.35 (s, 1H), 8.34 (s, 1H), 8.16 (s, 1H), 7.99 (s, 1H), 7.75 (d,  $J = 9.0$  Hz, 1H), 7.60 – 7.54 (m, 1H), 7.21 (t,  $J = 7.2$  Hz, 1H), 3.75 – 3.58 (m, 3H), 3.33 – 3.18 (m, 2H), 2.50 – 2.45 (m, 2H), 2.08 – 2.03 (m, 2H).

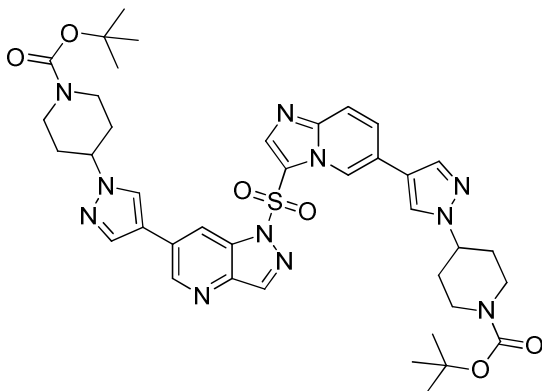
Example 67: Preparation of 1-[(6-chloro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Except for {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazoloborate pinacol ester was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(6-chloro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 24.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.19 (dd, *J* = 5.3, 4.4 Hz, 1H), 8.89 – 8.76 (m, 1H), 8.43 (d, *J* = 6.5 Hz, 1H), 8.36 (d, *J* = 7.0 Hz, 1H), 8.30 – 8.21 (m, 1H), 7.96 (d, *J* = 5.6 Hz, 1H), 7.91 (s, 1H), 7.72 – 7.58 (m, 1H), 7.54 – 7.39 (m, 1H), 4.46 – 4.16 (m, 3H), 3.06 – 2.79 (m, 2H), 2.31 – 2.13 (m, 2H), 2.09 – 1.90 (m, 2H), 1.49 (s, 9H).

Example 68: Preparation of 1-[(6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-{{1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



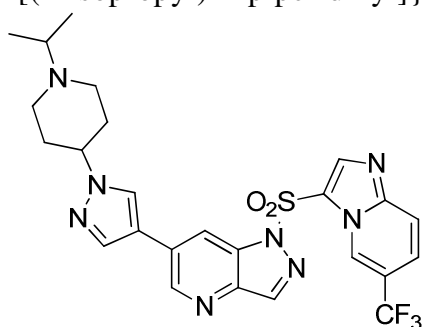
Into a microwave reaction tube were charged 150 mg compound of Example 67, 103 mg {1-[(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazoloborate pinacol ester and 103 mg

potassium carbonate, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 9.9 mg complex of 1,1'-bis(diphenylphosphino) ferrocene palladium (II) dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed.

5 The microwave tube was placed into a microwave reactor, reacted at 90°C for 10 minutes, the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound (m=159 mg, yield: 80%).

10 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.19 (s, 1H), 8.86 (d, *J* = 1.8 Hz, 1H), 8.46 (s, 1H), 8.33 (d, *J* = 0.8 Hz, 1H), 8.28 (s, 1H), 7.96 (s, 1H), 7.90 (s, 1H), 7.85 (s, 1H), 7.79 (s, 1H), 7.75 – 7.71 (m, 1H), 7.64 (dd, *J* = 9.3, 1.7 Hz, 1H), 4.44 – 4.21 (m, 6H), 3.01 – 2.83 (m, 4H), 2.28 – 2.16 (m, 4H), 2.09 – 1.94 (m, 4H), 1.50 (s, 18H).

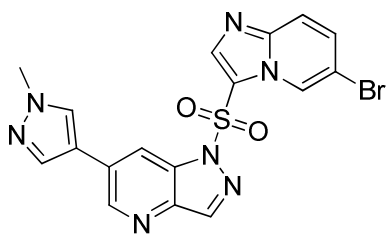
Example 69: 1-[(6-trifluoromethyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-  
15 6-{{1-[(1-isopropyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Except for the compound of Example 65 was used instead of the compound of  
Example 45, compound 1-[(6-trifluoromethyl-imidazo[1,2-a]  
pyridine)-3-sulfonyl]-6-{{1-[(1-isopropyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,  
20 3-b]pyridine was prepared by the same process as Example 59.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.53 (s, 1H), 8.87 (d, *J* = 1.8 Hz, 1H), 8.46 (s, 1H), 8.40 (s, 1H), 8.37 (s, 1H), 8.03 (s, 1H), 7.95 (s, 1H), 7.86 (d, *J* = 9.4 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 4.72 – 4.55 (m, 1H), 3.71 – 3.57 (m, 2H), 3.57 – 3.42 (m, 1H), 3.06 – 2.79 (m, 2H), 2.31 – 2.13 (m, 2H), 2.09 – 1.90 (m, 2H), 1.49 (s, 3H), 1.48 (s, 3H).

25 Example 70: Preparation of 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

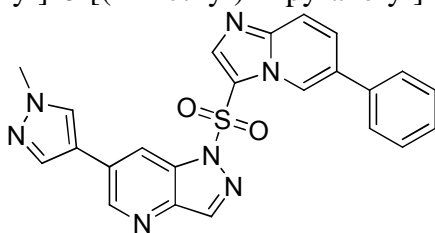


Except for (6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl chloride was used instead of (6-chloro-imidazo[1,2-a]pyridine)-3-sulfonyl chloride, compound 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-

pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 24.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.28 (dd,  $J = 1.7, 1.0$  Hz, 1H), 8.86 (d,  $J = 1.9$  Hz, 1H), 8.44 (dd,  $J = 1.8, 0.8$  Hz, 1H), 8.37 (d,  $J = 0.8$  Hz, 1H), 8.26 (s, 1H), 7.95 (d,  $J = 0.7$  Hz, 1H), 7.86 (s, 1H), 7.63 (dd,  $J = 9.5, 0.9$  Hz, 1H), 7.59 (dd,  $J = 9.5, 1.7$  Hz, 1H), 4.03 (s, 1H).

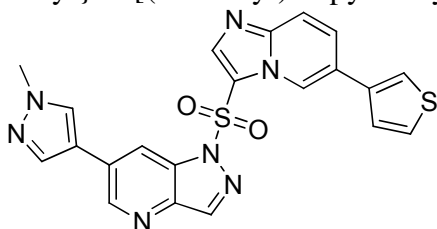
Example 71: Preparation of 1-[(6-phenyl-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Into a microwave reaction tube were charged 80 mg compound of Example 70, 25.7 mg phenylboronic acid and 87 mg potassium carbonate, 2 ml dioxane, 1 ml ethanol and 1 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 8.6 mg complex of 1,1'-bis(diphenylphosphino) ferrocene palladium (II) dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reacted at 90°C for 30 minutes, the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound (m=83 mg, yield: 86%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.27 (t,  $J = 1.3$  Hz, 1H), 8.86 (d,  $J = 1.9$  Hz, 1H), 8.48 (dd,  $J = 1.8, 0.8$  Hz, 1H), 8.35 (m, 2H), 7.95 (d,  $J = 0.7$  Hz, 1H), 7.85 (s, 1H), 7.78 (m, 2H), 7.61 (m, 2H), 7.50 (m, 3H), 4.04 (s, 3H).

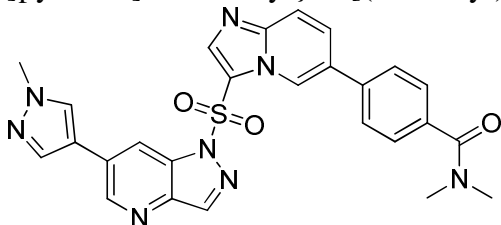
Example 72: Preparation of 1-{{6-(3-thiophene)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for thiophene-3-boronic acid was used instead of phenylboronic acid , compound 1-{{6-(3-thiophene)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.30 (s, 1H), 8.86 (d, J = 1.8 Hz, 1H), 8.48 (dd, J = 1.8, 0.8 Hz, 1H), 8.34 (d, J = 0.7 Hz, 1H), 8.32 (s, 1H), 7.95 (d, J = 0.6 Hz, 1H), 7.86 (s, 1H), 7.76 (d, J = 1.6 Hz, 2H), 7.57 (dd, J = 2.9, 1.4 Hz, 1H), 7.50 (dd, J = 5.0, 2.9 Hz, 1H), 7.43 (dd, J = 5.0, 1.4 Hz, 1H), 4.04 (s, 3H).

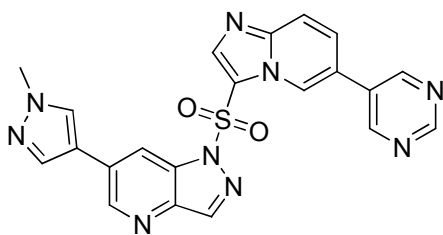
Example 73: Preparation of 1-{{6-(4-dimethylaminocarbonylphenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-dimethylaminocarbonylphenylboronic acid was used instead of phenylboronic acid , compound 1-{{6-(4-dimethylaminocarbonylphenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.30 (dd, J = 1.5, 1.0 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.48 (dd, J = 1.8, 0.8 Hz, 1H), 8.35 (m, 2H), 7.94 (d, J = 0.6 Hz, 1H), 7.86 (s, 1H), 7.81 (dd, J = 9.3, 0.9 Hz, 1H), 7.76 (dd, J = 9.3, 1.7 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 4.03 (s, 3H), 3.12 (d, J = 40.7 Hz, 6H).

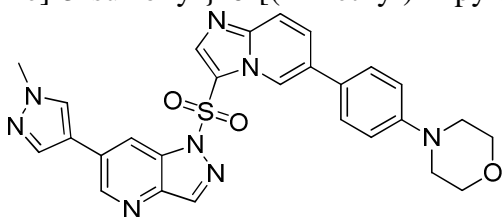
Example 74: Preparation of 1-{{6-(5-pyrimidine)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for pyrimidine-5-boronic acid was used instead of phenylboronic acid, compound 1-[[6-(5-pyrimidine)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.43 (dd, J = 1.8, 1.1 Hz, 1H), 9.36 (s, 1H), 9.07 (s, 2H), 8.87 (d, J = 1.9 Hz, 1H), 8.46 (dd, J = 1.8, 0.8 Hz, 1H), 8.35 (m, 2H), 7.95 (d, J = 0.8 Hz, 1H), 7.90 (dd, J = 9.4, 0.9 Hz, 1H), 7.87 (s, 1H), 7.73 (dd, J = 9.3, 1.9 Hz, 1H), 4.04 (s, 3H).

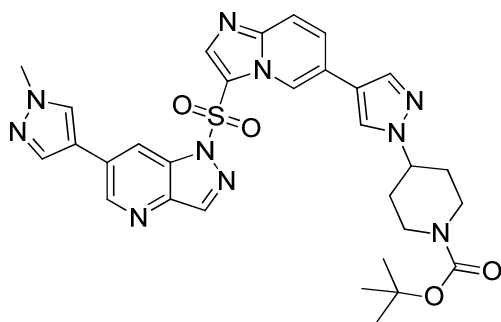
Example 75: Preparation of 1-[[6-(4-morpholinylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-morpholinylphenylboronic acid was used instead of phenylboronic acid, compound 1-[[6-(4-morpholinylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.19 (t, J = 1.2 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.49 (dd, J = 1.8, 0.7 Hz, 1H), 8.34 (d, J = 0.7 Hz, 1H), 8.32 (s, 1H), 7.95 (s, 1H), 7.86 (s, 1H), 7.74 (d, J = 1.3 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.03 (s, 3H), 3.91 (m, 4H), 3.26 (m, 4H).

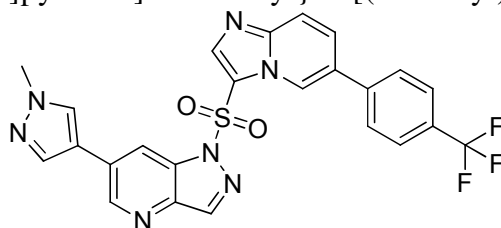
Example 76: Preparation of 1-((6-((1-((1-t-butoxycarbonyl)-4-piperidinyl))-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 1-[(1-t-butoxycarbonyl)-4-piperidinyl]-pyrazolo-4-pinacol ester was used instead of phenylboronic acid, compound 1-[(6-[(1-[(1-t-butoxycarbonyl)-4-piperidinyl]-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.17 (s, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.46 (m, 1H), 8.33 (s, 1H), 8.28 (s, 1H), 7.95 (s, 1H), 7.87 (s, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.72 (d, J = 9.4 Hz, 1H), 7.63 (dd, J = 9.3, 1.7 Hz, 1H), 4.35 (m, 3H), 4.04 (s, 3H), 2.95 (m, 2H), 2.20 (m, 2H), 2.00 (m, 4.4 Hz, 2H), 1.50 (s, 9H).

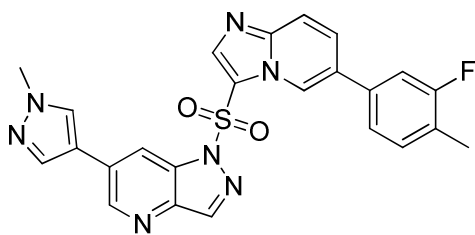
Example 77: Preparation of 1-[(6-(4-trifluoromethylphenyl)-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-trifluoromethylphenylboronic acid was used instead of phenylboronic acid, compound 1-[(6-(4-trifluoromethylphenyl)-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.34 (s, 1H), 8.87 (d, J = 1.8 Hz, 1H), 8.48 (s, 1H), 8.35 (s, 2H), 7.96 (s, 1H), 7.85 (m, 2H), 7.76 (m, 5H), 4.04 (s, 3H).

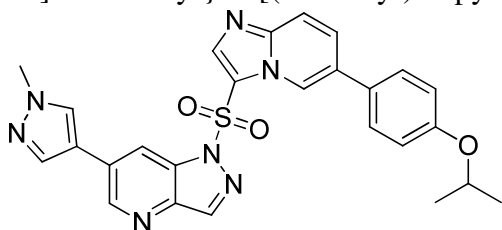
Example 78: Preparation of 1-[(6-(3-fluoro-4-methylphenyl)-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3-fluoro-4-methylphenylboronic acid was used instead of phenylboronic acid, compound 1-{[6-(3-fluoro-4-methylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.25 (s, 1H), 8.86 (d, J = 1.7 Hz, 1H), 8.47 (s, 1H), 8.34 (d, J = 7.3 Hz, 2H), 7.94 (s, 1H), 7.86 (s, 1H), 7.78 (d, J = 9.3 Hz, 1H), 7.72 (dd, J = 9.4, 1.7 Hz, 1H), 7.29 (m, 3H), 4.04 (s, 3H), 2.36 (d, J = 1.6 Hz, 3H).

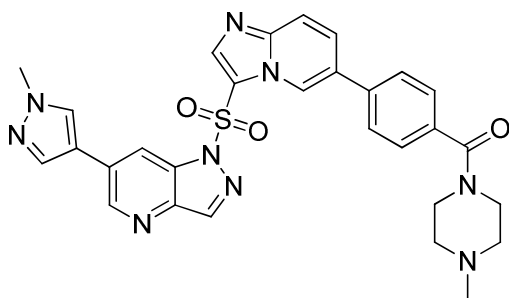
Example 79: Preparation of 1-{[6-(4-isopropoxyl)phenyl]-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-isopropoxylphenylboronic acid was used instead of phenylboronic acid, compound 1-{[6-(4-isopropoxyl)phenyl]-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.27 (m, 1H), 8.85 (d, J = 1.9 Hz, 1H), 8.47 (dd, J = 1.8, 0.8 Hz, 1H), 8.34 (m, 2H), 7.94 (d, J = 0.6 Hz, 1H), 7.85 (s, 1H), 7.76 (m, 2H), 7.39 (t, J = 7.9 Hz, 1H), 7.14 (t, J = 4.9 Hz, 2H), 6.98 (dd, J = 8.0, 2.1 Hz, 1H), 4.66 (dt, J = 12.1, 6.1 Hz, 1H), 4.03 (s, 3H), 1.41 (d, J = 6.1 Hz, 6H).

Example 80: Preparation of 1-{[6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

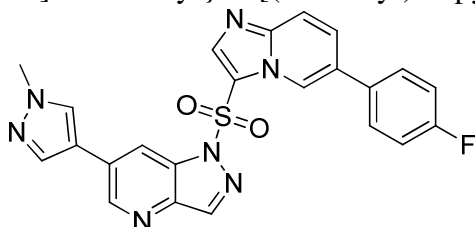


Except for 4-(4-methylpiperazine-1-carbonyl)phenylboronic acid was used instead of phenylboronic acid, compound 1-[[6-((4-methylpiperazine-1-carbonyl)phenyl)-imidazo[1,2-a]pyridine-3-sulfonyl]-6-((1-methyl)-4-

5 pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.31 (m, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.47 (dd, J = 1.8, 0.8 Hz, 1H), 8.36 (d, J = 0.8 Hz, 1H), 8.34 (s, 1H), 7.95 (d, J = 0.6 Hz, 1H), 7.87 (s, 1H), 7.81 (dd, J = 9.3, 0.8 Hz, 1H), 7.76 (dd, J = 9.3, 1.7 Hz, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 4.04 (s, 3H), 3.86 (s, 2H), 3.54 (s, 2H), 2.50 (d, J = 47.2 Hz, 4H),  
10 2.38 (s, 3H).

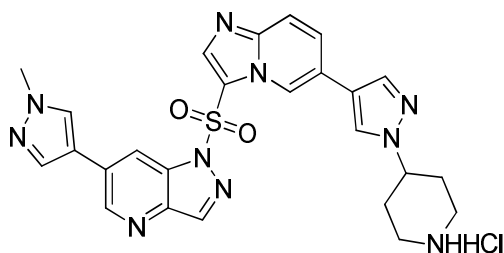
Example 81: Preparation of 1-[[6-(4-fluorophenyl)-imidazo[1,2-a]pyridine-3-sulfonyl]-6-((1-methyl)-4-pyrazolyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 4-fluorophenylboronic acid was used instead of phenylboronic acid,  
15 compound 1-[[6-(4-fluorophenyl)-imidazo[1,2-a]pyridine-3-sulfonyl]-6-((1-methyl)-4-pyrazolyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.24 (s, 1H), 8.86 (d, J = 1.8 Hz, 0H), 8.48 (d, J = 1.1 Hz, 1H), 8.34 (d, J = 7.2 Hz, 2H), 7.95 (s, 1H), 7.86 (s, 1H), 7.79 (d, J = 9.3 Hz, 1H), 7.72  
20 (dd, J = 9.3, 1.8 Hz, 1H), 7.58 (dd, J = 8.7, 5.1 Hz, 2H), 7.21 (t, J = 8.6 Hz, 2H), 4.04 (s, 3H).

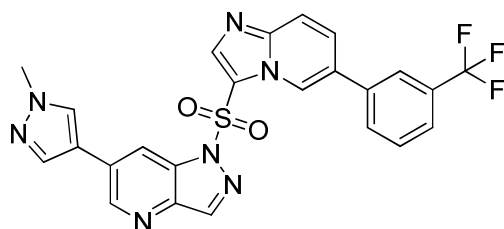
Example 82: Preparation of 1-[[6-([1-(4-piperidinyl)]-4-pyrazolyl)-imidazo[1,2-a]pyridine-3-sulfonyl]-6-((1-methyl)-4-pyrazolyl)-1-H-pyrazolo[4,3-b]pyridine chloride



Fifty milligrams compound of Example 76 was dissolved in 5 ml dioxane saturated with hydrochloric acid, stirred for 30 minutes at room temperature. The reaction was completed, and filtered to obtain filter cake, which was washed three times by ether immersion, vacuum dried to obtain the target compound (m=36 mg, yield: 86%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.05 (d, J = 1.8 Hz, 1H), 8.96 (s, 1H), 8.75 (s, 1H), 8.65 (s, 1H), 8.60 (s, 2H), 8.36 (s, 1H), 8.27 (s, 1H), 7.96 (d, J = 13.6 Hz, 2H), 7.90 (d, J = 8.9 Hz, 1H), 4.51 (m, 2H), 3.95 (s, 3H), 3.40 (m, 3H), 3.06 (m, 3H).

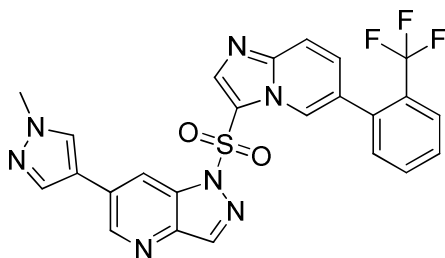
Example 83: Preparation of 1-{{6-(3-trifluoromethylphenyl)-imidazo[1,2-a]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3-trifluoromethylphenylboronic acid was used instead of phenylboronic acid, compound 1-{{6-(3-trifluoromethylphenyl)-imidazo[1,2-a]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.35 (s, 1H), 8.87 (d, J = 1.9 Hz, 1H), 8.47 (d, J = 1.0 Hz, 1H), 8.36 (s, 2H), 7.94 (s, 1H), 7.84 (m, 4H), 7.76 (m, 2H), 7.67 (t, J = 7.8 Hz, 1H), 4.04 (s, 3H).

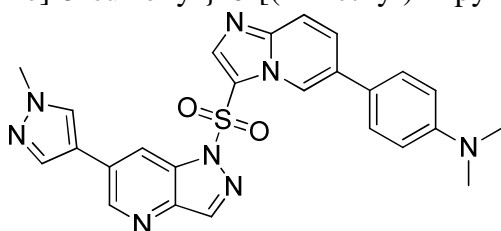
Example 84: Preparation of 1-{{6-(2-trifluoromethylphenyl)-imidazo[1,2-a]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 2-trifluoromethylphenylboronic acid was used instead of phenylboronic acid, compound 1-([6-(2-trifluoromethylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl)-6-((1-methyl-4-pyrazolyl)-1H-pyrazolo[4,3-b]pyridin-1-yl)pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.10 (s, 1H), 8.85 (d, J = 1.9 Hz, 1H), 8.43 (dd, J = 1.8, 0.8 Hz, 1H), 8.35 (s, 1H), 8.30 (d, J = 0.7 Hz, 1H), 7.92 (d, J = 0.7 Hz, 1H), 7.85 (m, 2H), 7.75 (dd, J = 9.2, 0.8 Hz, 1H), 7.64 (m, 2H), 7.49 (m, 1H), 7.40 (d, J = 7.2 Hz, 1H), 4.03 (s, 2H).

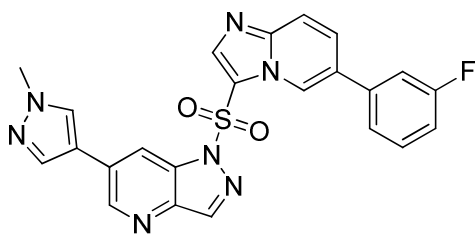
Example 85: Preparation of 1-([6-(4-dimethylaminophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl)-6-((1-methyl-4-pyrazolyl)-1H-pyrazolo[4,3-b]pyridin-1-yl)pyridine



Except for 4-dimethylaminophenylboronic acid was used instead of phenylboronic acid, compound 1-([6-(4-dimethylaminophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl)-6-((1-methyl-4-pyrazolyl)-1H-pyrazolo[4,3-b]pyridin-1-yl)pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.14 (t, J = 1.3 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.49 (dd, J = 1.9, 0.8 Hz, 1H), 8.35 (d, J = 0.8 Hz, 1H), 8.31 (s, 1H), 7.96 (d, J = 0.6 Hz, 1H), 7.86 (s, 1H), 7.73 (dd, J = 3.5, 2.0 Hz, 2H), 7.46 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 4.03 (s, 3H), 3.03 (s, 6H).

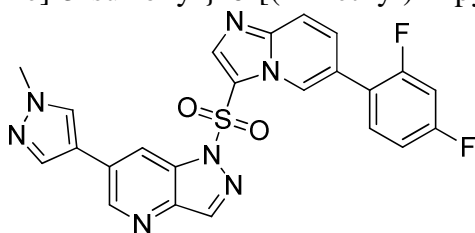
Example 86: Preparation of 1-([6-(3-fluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl)-6-((1-methyl-4-pyrazolyl)-1H-pyrazolo[4,3-b]pyridin-1-yl)pyridine



Except for 3-fluorophenylboronic acid was used instead of phenylboronic acid, compound 1-{{[6-(3-fluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.29 (dd, J = 1.7, 1.0 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.48 (dd, J = 1.9, 0.9 Hz, 1H), 8.36 (d, J = 0.8 Hz, 1H), 8.34 (s, 1H), 7.94 (d, J = 0.7 Hz, 1H), 7.86 (s, 1H), 7.80 (dd, J = 9.3, 1.0 Hz, 1H), 7.74 (dd, J = 9.3, 1.8 Hz, 1H), 7.49 (m, 1H), 7.41 (m, 1H), 7.32 (m, 1H), 7.18 (tdd, J = 8.5, 2.6, 1.0 Hz, 1H), 4.04 (s, 3H).

Example 87: Preparation of 1-{{[6-(2,4-difluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

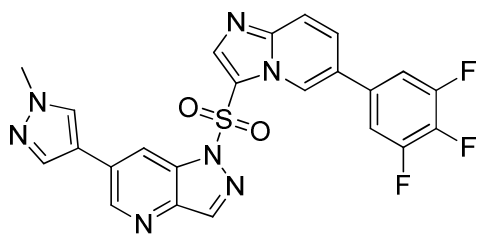


Except for 2,4-difluorophenylboronic acid was used instead of phenylboronic acid, compound

1-{{[6-(2,4-difluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.24 (s, 1H), 8.86 (d, J = 1.8 Hz, 1H), 8.46 (dd, J = 1.8, 0.8 Hz, 1H), 8.35 (d, J = 0.8 Hz, 2H), 7.94 (d, J = 0.5 Hz, 1H), 7.86 (s, 1H), 7.79 (dd, J = 9.3, 0.8 Hz, 1H), 7.67 (dt, J = 9.3, 1.6 Hz, 1H), 7.48 (td, J = 8.6, 6.2 Hz, 1H), 7.02 (m, 2H), 4.04 (s, 3H).

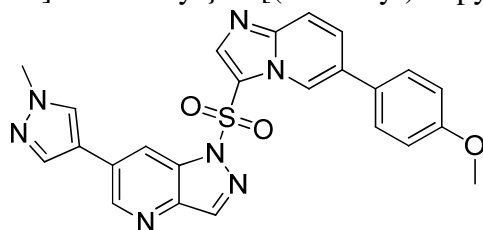
Example 88: Preparation of 1-{{[6-(3,4,5-trifluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3,4,5-trifluorophenylboronic acid was used instead of phenylboronic acid, compound 1-[[6-(3,4,5-trifluorophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.27 (s, 1H), 8.87 (d,  $J$  = 1.8 Hz, 1H), 8.47 (s, 1H), 8.34 (d,  $J$  = 6.4 Hz, 2H), 7.95 (s, 1H), 7.86 (s, 1H), 7.81 (d,  $J$  = 9.3 Hz, 1H), 7.66 (dd,  $J$  = 9.3, 1.8 Hz, 1H), 7.26 (m, 2H), 4.04 (s, 3H).

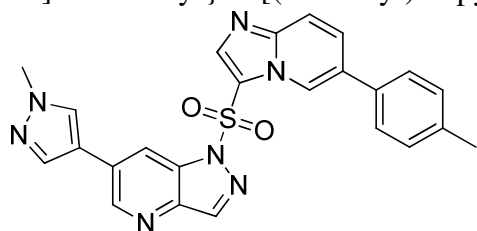
Example 89: Preparation of 1-[[6-(4-methoxyphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-methoxyphenylboronic acid was used instead of phenylboronic acid, compound 1-[[6-(4-methoxyphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.20 (t,  $J$  = 1.3 Hz, 1H), 8.86 (d,  $J$  = 1.9 Hz, 1H), 8.48 (m, 1H), 8.35 (s, 1H), 8.32 (s, 1H), 7.95 (s, 1H), 7.85 (s, 1H), 7.75 (m, 2H), 7.54 (d,  $J$  = 8.8 Hz, 2H), 7.02 (d,  $J$  = 8.8 Hz, 2H), 4.04 (s, 3H), 3.89 (s, 3H).

Example 90: Preparation of 1-[[6-(4-methylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

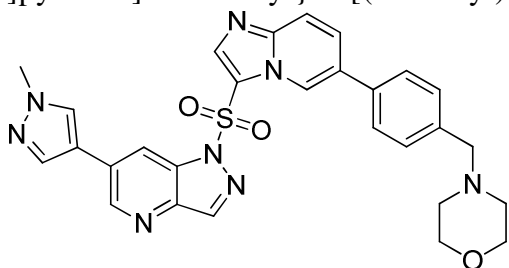


Except for 4-methylphenylboronic acid was used instead of phenylboronic acid,

compound 1-{{6-(4-methylphenyl)-imidazo[1,2-a]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.24 (t, J = 1.3 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.48 (m, 1H), 8.34 (d, J = 7.4 Hz, 2H), 7.95 (s, 1H), 7.85 (s, 1H), 7.76 (d, J = 1.3 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.04 (s, 3H), 2.44 (s, 3H).

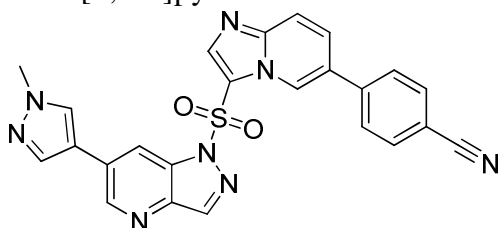
Example 91: Preparation of 1-{{6-(4-morpholinomethylphenyl)-imidazo[1,2-a]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-morpholinomethylphenylboronic acid was used instead of phenylboronic acid, compound 1-{{6-(4-morpholinomethylphenyl)-imidazo[1,2-a]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.30 (s, 1H), 8.88 (d, J = 1.6 Hz, 1H), 8.50 (d, J = 1.8 Hz, 1H), 8.37 (s, 1H), 8.34 (s, 1H), 7.97 (s, 1H), 7.88 (s, 1H), 7.79 (t, J = 1.5 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 4.06 (s, 3H), 3.78 (m, 4H), 3.60 (s, 2H), 2.52 (m, 4H).

Example 92: Preparation of 1-{{6-(4-cyanophenyl)-imidazo[1,2-a]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

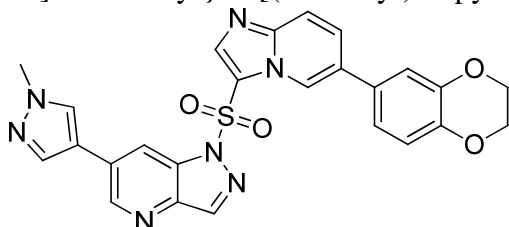


Except for 4-cyanophenylboronic acid was used instead of phenylboronic acid, compound 1-{{6-(4-cyanophenyl)-imidazo[1,2-a]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the

same process as Example 71.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.37 (s, 1H), 8.87 (d,  $J = 1.9$  Hz, 1H), 8.47 (dd,  $J = 1.5, 0.5$  Hz, 1H), 8.34 (s, 2H), 7.95 (s, 1H), 7.84 (m, 4H), 7.75 (m, 3H), 4.04 (s, 3H).

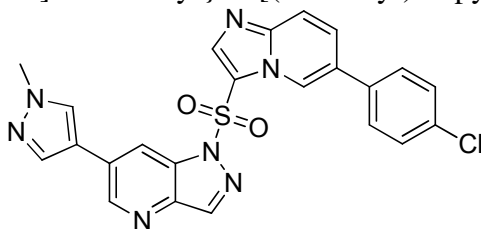
Example 93: Preparation of 1-{{6-[6-(1,4-benzodioxanyl)]-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for (1,4-benzodioxanyl)-6-boronic acid was used instead of phenylboronic acid, compound 1-{{6-[6-(1,4-benzodioxanyl)]-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.18 (s, 1H), 8.85 (d,  $J = 1.8$  Hz, 1H), 8.47 (d,  $J = 1.1$  Hz, 1H), 8.35 (s, 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.85 (s, 1H), 7.75 (d,  $J = 9.4$  Hz, 1H), 7.70 (dd,  $J = 9.2, 1.6$  Hz, 1H), 7.12 (d,  $J = 2.1$  Hz, 1H), 7.08 (dd,  $J = 8.3, 2.3$  Hz, 1H), 6.98 (d,  $J = 8.3$  Hz, 1H), 4.34 (s, 4H), 4.03 (s, 3H).

Example 94: Preparation of 1-{{6-(4-chlorophenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

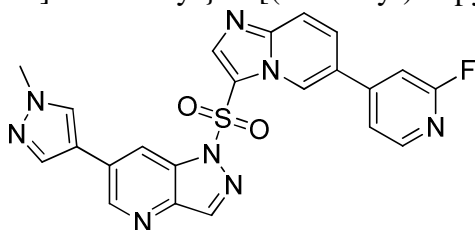


Except for 4-chlorophenylboronic acid was used instead of phenylboronic acid, compound 1-{{6-(4-chlorophenyl)-imidazo[1,2-a]pyridine}-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.26 (m, 1H), 8.86 (d,  $J = 1.8$  Hz, 1H), 8.47 (m, 1H), 8.34 (d,  $J = 5.4$  Hz, 2H), 7.95 (s, 1H), 7.85 (s, 1H), 7.79 (dd,  $J = 9.3$  Hz, 0.9 Hz, 1H), 7.72 (dd,  $J = 9.3, 1.7$  Hz, 1H), 7.55 (m, 2H), 7.48 (m, 2H), 4.04 (s, 3H).

Example 95: Preparation of 1-{{6-(3-fluoro-4-pyridinyl)-imidazo[1,2-a]

pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

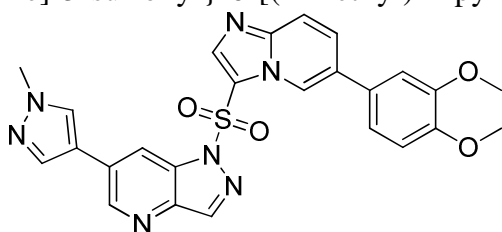


Except for 3-fluoro-pyridine-4-boronic acid was used instead of phenylboronic acid, compound 1-[[6-(3-fluoro-4-pyridinyl)-imidazo[1,2-a]

5 pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.47 (dd, J = 1.7, 1.0 Hz, 1H), 8.89 (d, J = 1.9 Hz, 1H), 8.49 (dd, J = 1.8, 0.9 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H), 8.37 (s, 2H), 7.97 (d, J = 0.4 Hz, 1H), 7.89 (m, 2H), 7.78 (dd, J = 9.3, 1.8 Hz, 1H), 7.51 (dt, J = 5.2, 1.4 Hz, 1H), 7.23  
10 (t, J = 1.7 Hz, 1H), 4.06 (s, 3H).

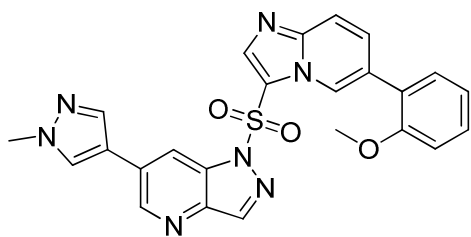
Example 96: Preparation of 1-[[6-(3,4-dimethoxyphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3,4-dimethoxyphenylboronic acid was used instead of phenylboronic acid, compound 1-[[6-(3,4-dimethoxyphenyl)-imidazo[1,2-a]  
15 pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.23 (t, J = 1.2 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.47 (dd, J = 1.8, 0.6 Hz, 1H), 8.33 (s, 2H), 7.94 (s, 1H), 7.85 (s, 1H), 7.75 (m, 2H), 7.16 (dd, J = 8.3, 2.1 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.03 (s, 3H), 3.99 (s,  
20 3H), 3.97 (s, 3H).

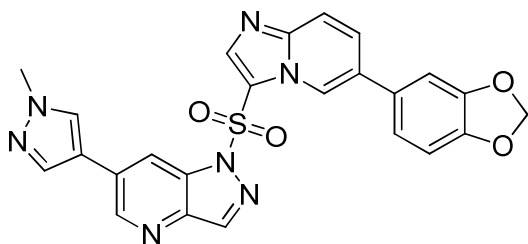
Example 97: Preparation of 1-[[6-(2-methoxyphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 2-methoxyphenylboronic acid was used instead of phenylboronic acid, compound 1-{{[6-(2-methoxyphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.20 (t, J = 1.3 Hz, 1H), 8.85 (d, J = 1.9 Hz, 1H), 8.47 (dd, J = 1.9, 0.8 Hz, 1H), 8.34 (m, 2H), 7.93 (d, J = 0.7 Hz, 1H), 7.83 (s, 1H), 7.73 (dd, J = 2.5, 1.3 Hz, 2H), 7.43 (m, 1H), 7.35 (dd, J = 7.5, 1.7 Hz, 1H), 7.06 (m, 2H), 4.03 (s, 3H), 3.85 (s, 3H).

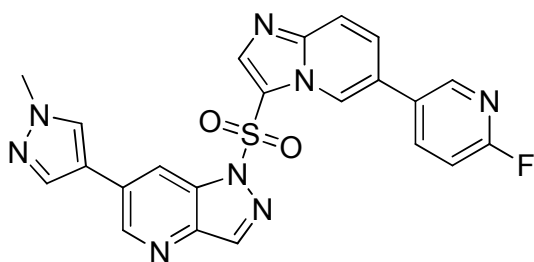
Example 98: Preparation of 1-{{[6-[5-(1,2-methylenedioxyphenyl)]-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 5-(1,2-methylenedioxyphenyl)boronic acid was used instead of phenylboronic acid, compound 1-{{[6-[5-(1,2-methylenedioxyphenyl)]-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.18 (dd, J = 1.6, 1.0 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.47 (dd, J = 1.8, 0.8 Hz, 1H), 8.35 (d, J = 0.7 Hz, 1H), 8.32 (s, 1H), 7.94 (d, J = 0.6 Hz, 1H), 7.85 (m, 1H), 7.75 (dd, J = 9.3, 0.9 Hz, 1H), 7.69 (dd, J = 9.4, 1.9 Hz, 1H), 7.07 (m, 2H), 6.93 (d, J = 8.5 Hz, 1H), 6.07 (s, 2H), 4.04 (s, 3H).

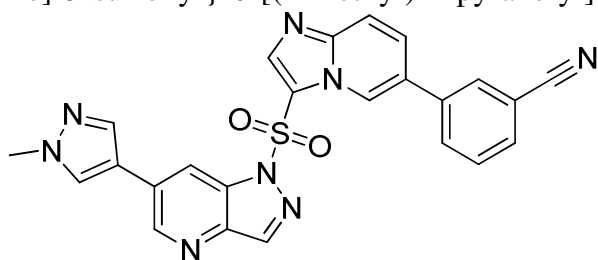
Example 99: Preparation of 1-{{[6-(2-fluoro-5-pyridinyl)-imidazo[1,2-a]pyridine]-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 2-fluoro-pyridine-5-boronic acid was used instead of phenylboronic acid, compound 1-[[6-(2-fluoro-5-pyridinyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.34 (s, 1H), 8.89 (d, J = 1.8 Hz, 1H), 8.53 (d, J = 2.6 Hz, 1H), 8.48 (d, J = 1.0 Hz, 1H), 8.36 (s, 2H), 8.08 (ddd, J = 8.2, 7.5, 2.6 Hz, 1H), 7.97 (s, 1H), 7.87 (m, 2H), 7.72 (dd, J = 9.3, 1.8 Hz, 1H), 7.15 (dd, J = 8.7, 3.0 Hz, 1H), 4.06 (s, 3H).

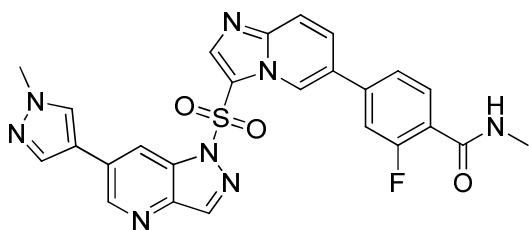
Example 100: Preparation of 1-[[6-(3-cyanophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3-cyanophenylboronic acid was used instead of phenylboronic acid, compound 1-[[6-(3-cyanophenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.33 (s, 1H), 8.87 (d, J = 1.8 Hz, 1H), 8.47 (dd, J = 1.8, 0.8 Hz, 1H), 8.35 (m, 2H), 7.95 (d, J = 2.9 Hz, 1H), 7.87 (m, 4H), 7.78 (dt, J = 7.8, 1.3 Hz, 1H), 7.72 (dd, J = 9.4, 1.8 Hz, 1H), 7.67 (m, 1H), 4.04 (s, 3H).

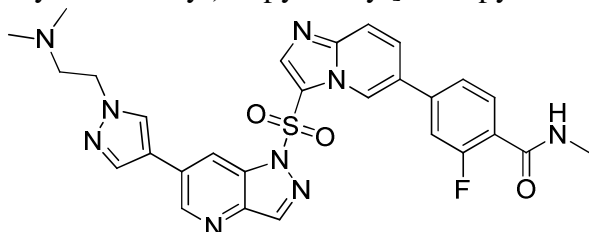
Example 101: Preparation of 1-[[6-(3-fluoro-4-methylaminocarbonylphenyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 3-fluoro-4-methylaminocarbonylphenylboronic acid was used instead of phenylboronic acid, compound 1-((6-(3-fluoro-4-methylaminocarbonylphenyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.34 (d, J = 1.5 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.47 (d, J = 1.9 Hz, 1H), 8.35 (s, 1H), 8.34 (s, 1H), 8.25 (t, J = 8.2 Hz, 1H), 7.93 (s, 1H), 7.86 (s, 1H), 7.83 (dd, J = 9.3, 0.9 Hz, 1H), 7.75 (dd, J = 9.4, 1.8 Hz, 1H), 7.53 (dd, J = 8.2, 1.8 Hz, 1H), 7.41 (dd, J = 12.6, 1.8 Hz, 1H), 6.84 (s, 1H), 4.04 (s, 3H), 3.10 (d, J = 5.1 Hz, 3H).

Example 102: Preparation of 1-((6-(3-fluoro-4-methylaminocarbonylphenyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-[(2-dimethylaminoethyl)-4-pyrazolyl]-1H-pyrazolo[4,3-b]pyridine

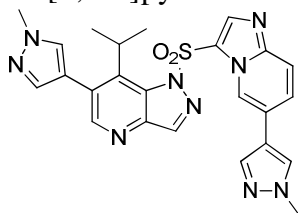


Except for 2-dimethylaminoethyl-1H-pyrazolo-4-borrate pinacol ester was used instead of 1-methyl-1H-pyrazolo-4-boronic acid pinacol ester, compound 1-((6-(3-fluoro-4-methylaminocarbonylphenyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-[(2-dimethylaminoethyl)-4-pyrazolyl]-1H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 71.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.33 (d, J = 1.5 Hz, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.46 (d, J = 1.9 Hz, 1H), 8.35 (s, 1H), 8.33 (s, 1H), 8.25 (t, J = 8.1 Hz, 1H), 7.91 (s, 1H), 7.84 (s, 1H), 7.83 (dd, J = 9.3, 0.9 Hz, 1H), 7.75 (dd, J = 9.4, 1.8 Hz, 1H), 7.53 (dd, J = 8.1, 1.8 Hz, 1H), 7.41 (dd, J = 12.6, 1.8 Hz, 1H), 6.84 (s, 1H), 4.10 (t, J = 6.5 Hz, 2H), 3.10 (d, J = 5.1 Hz, 3H), 2.64 (t, J = 6.5 Hz, 2H), 2.18 (s, 6H).

Example 103: Preparation of 1-((6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-[(2-dimethylaminoethyl)-4-pyrazolyl]-1H-pyrazolo[4,3-b]pyridine

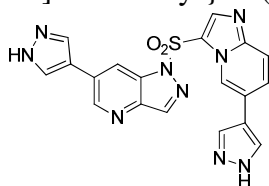
[1,2-a]pyridine)-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-7-isopropyl-1-H-pyrazolo[4,3-b]pyridine



Fifty milligrams compound 27, 61 mg zinc bis(isopropyl)sulfinate were dissolved into 5 ml dimethyl sulfoxide, 32  $\mu$ l t-butyl hydroperoxide was added with vigorous agitation, reaction was conducted at 50°C for 12 hours. After the reaction was completed, the reactant liquid was cooled to room temperature, 50 ml saturated sodium bicarbonate was added, extracted three times with 30 ml ethyl acetate. The organic layer was dried over anhydrous sodium sulfate then concentrated, and isolated by flash preparative chromatography to obtain the target compound 103 (m=15 mg, yield: 30%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.44 (s, 1H), 8.89 (s, 1H), 8.48 (s, 1H), 8.38 (s, 1H), 7.90 (d, J = 0.9 Hz, 1H), 7.82 (s, 1H), 7.79 (d, J = 9.3 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.52 (s, 1H), 7.44 (s, 1H), 4.04 (s, 3H), 4.00 (s, 3H), 3.38 (m, 1H), 1.27 (d, J = 6.9 Hz, 6H).

Example 104: Preparation of 1-[[6-(4-pyrazolyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-(4-pyrazolyl)-1-H-pyrazolo[4,3-b]pyridine



Eighty milligrams sodium hydride was dissolved in 30 ml anhydrous tetrahydrofuran, stirred for 5 minutes at room temperature. Four hundred and forty milligrams 6-bromoindazole was dissolved in 30 ml anhydrous tetrahydrofuran, then slowly and dropwisely added into the tetrahydrofuran solution of sodium hydride, stirred for 30 minutes at room temperature after the addition was completed. Seven hundred and twenty-three milligrams 6-bromoimidazo[1,2-a]pyridine-3-sulfonyl chloride was dissolved in 30 ml anhydrous tetrahydrofuran, then slowly and dropwisely added into the reactant liquid, stirred overnight at room temperature after the addition was done, the reaction was completed. Tetrahydrofuran was removed by evaporation, and the remainder

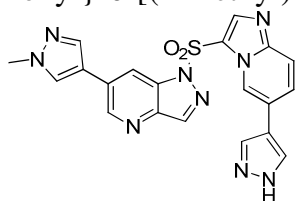
was dissolved in dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain

1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-bromo-1-H-pyrazolo[4,3-b]pyridine (m=755 mg, yield: 74.3%). ESI (m/z): 458.0 [M+H]<sup>+</sup>.

Into a microwave reaction tube were disposed 80 mg 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-bromo-1-H-pyrazolo[4,3-b]pyridine, 113 mg 1-t-butoxycarbonyl-1H-pyrazolo-4-boronic acid pinacol ester and 97 mg potassium carbonate, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 7.2 mg 1,1'-bis(diphenylphosphino) ferrocene palladium (II)dichloromethane complex was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reaction was conducted at a temperature of 120°C for 30 minutes, the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated. The concentrated solid was dissolved in 10 ml dioxane saturated with hydrochloric acid, stirred at room temperature for 3 hours, then evaporated to remove the organic phase, and isolated by flash preparative chromatography to obtain the target compound 104 (m=64 mg, yield: 85%). ESI (m/z): 432.0 [M+H]<sup>+</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.25 (s, 1H), 8.92 (s, 1H), 8.55 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.09 (s, 2H), 7.98 (s, 2H), 7.77 (d, J = 9.1 Hz, 1H), 7.69 (d, J = 9.5 Hz, 1H).

Example 105: Preparation of 1-[[6-(4-pyrazolyl)-imidazo[1,2-a]pyridine]-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

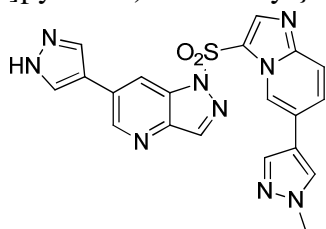


Except for pyrazolo-4-boronic acid was used instead of phenylboronic acid, compound 1-[[6-(4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process

as Example 71.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.05 (d,  $J = 1.9$  Hz, 1H), 8.97 (s, 1H), 8.76 (d,  $J = 0.9$  Hz, 1H), 8.64 (s, 1H), 8.61 – 8.58 (m, 1H), 8.57 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.34 (s, 1H), 8.24 (d,  $J = 0.8$  Hz, 1H), 7.96 (dd,  $J = 9.3, 1.8$  Hz, 1H), 7.93 (s, 1H), 7.88 (dd,  $J = 9.3, 1.0$  Hz, 1H), 3.94 (s, 3H).

Example 106: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-(4-pyrazolyl)-1-H-pyrazolo[4,3-b]pyridine



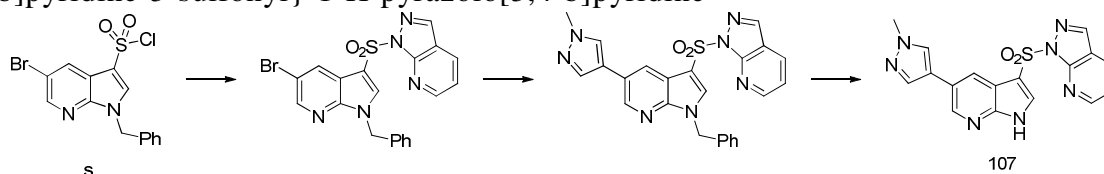
One hundred milligrams sodium hydride was dissolved in 30 ml anhydrous tetrahydrofuran, stirred for 5 minutes at room temperature. Five hundred and fifty milligrams 6-bromoindazole was dissolved in 30 ml anhydrous tetrahydrofuran, then slowly and dropwisely added into the tetrahydrofuran solution of sodium hydride, stirred for 30 minutes at room temperature after the addition was completed. Nine hundred and seven milligrams 6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine-3-sulfonyl chloride was dissolved in 30 ml anhydrous tetrahydrofuran, slowly and dropwisely added into the reactant liquid, stirred overnight at room temperature after the addition was done, the reaction was completed. Tetrahydrofuran was removed by evaporation, the remainder was dissolved in dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain compound 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-bromo-1-H-pyrazolo[4,3-b]pyridine (m=968 mg, yield: 76%). ESI ( $m/z$ ): 460.0, 458.0  $[\text{M}+\text{H}]^+$ .

Into a microwave reaction tube were disposed 100 mg 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-bromo-1-H-pyrazolo[4,3-b]pyridine, 77 mg 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester and 90 mg potassium carbonate, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 9 mg complex of 1,1'-bis(diphenylphosphino) ferrocene palladium (II)

dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reaction was conducted at a temperature of 120°C for 30 minutes, the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with  
 5 dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated. The concentrated solid was dissolved into 10 ml dioxane saturated with hydrochloric acid, stirred at room temperature for 3 hours, evaporated to remove the organic phase, and isolated by flash preparative chromatography to obtain the target compound 106 (m=80 mg, yield: 82%).

10  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.30 (s, 1H), 8.88 (dd,  $J = 1.9, 1.0$  Hz, 1H), 8.46 (d,  $J = 1.6$  Hz, 1H), 8.39 (s, 1H), 8.28 (s, 1H), 7.97 (s, 1H), 7.88 (s, 1H), 7.65 (d,  $J = 9.3$  Hz, 1H), 7.60 (d,  $J = 9.7$  Hz, 2H), 7.29 (s, 1H), 4.05 (s, 3H).

Example 107: Preparation of 1-((5-[(1-methyl)-4-pyrazolyl])-1-H-pyrrolo[2,3-b]pyridine-3-sulfonyl)-1-H-pyrazolo[3,4-b]pyridine

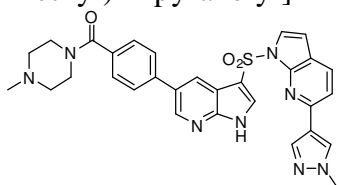


Eighty milligrams sodium hydride was dissolved in 30 ml anhydrous tetrahydrofuran, stirred for 5 minutes at room temperature. Two hundred and sixty-five milligrams 1-H-pyrazolo[3,4-b]pyridine was dissolved in 30 ml anhydrous tetrahydrofuran, then slowly and dropwisely added into the tetrahydrofuran solution of sodium hydride, stirred  
 20 for 30 minutes at room temperature after the addition was completed. Nine hundred and seven milligrams 1-benzyl-5-bromo-1-H-pyrrolo[2,3-b]pyridine-3-sulfonyl chloride was dissolved in 30 ml anhydrous tetrahydrofuran, slowly and dropwisely added into the reactant liquid, stirred overnight at room temperature after the addition was done, the reaction was completed. Tetrahydrofuran was removed by evaporation, the remainder was  
 25 dissolved in dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain compound 1-[(1-benzyl-5-bromo-pyrrolo[2,3-b]pyridine)-3-sulfonyl]-1-H-pyrazolo[3,4-b]pyridine (m=697 mg, yield: 67%). ESI (m/z): 470.0, 468.0  $[\text{M}+\text{H}]^+$ .

Into a microwave reaction tube were disposed 90 mg 1-[(1-benzyl-5-bromo-pyrrolo[2,3-b]pyridine)-3-sulfonyl]-1-H-pyrazolo[3,4-b]pyridine, 48 mg 1-methyl-1H-pyrazolo-4-borrate pinacol ester and 80 mg potassium carbonate, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 7.8 mg 1,1'-bis(diphenylphosphino) ferrocene palladium (II)dichloromethane complex was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reaction was conducted at a temperature of 120°C for 30 minutes, the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain 1-{(5-[(1-methyl)-4-pyrazolyl])-1-benzyl-pyrrolo[2,3-b]pyridine-3-sulfonyl}-1-H-pyrazolo[3,4-b]pyridine (m=90 mg, yield: 85%). ESI (m/z): 549.4 [M+H]<sup>+</sup>.

Fifty milligrams 1-{(5-[(1-methyl)-4-pyrazolyl])-1-benzyl-pyrrolo[2,3-b]pyridine-3-sulfonyl}-1-H-pyrazolo[3,4-b]pyridine and 17 mg 10% palladium on carbon was dissolved in 30 ml ethanol, reacted at 70°C under 20 psi hydrogen pressure, filtered to remove the palladium on carbon, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain compound 107 (m=38 mg, yield: 94%). ESI (m/z): 380.0 [M+H]<sup>+</sup>.

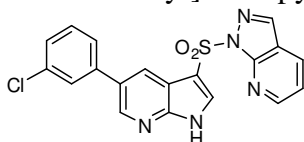
Example 108: Preparation of 1-{[6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-1-H-pyrrolo[2,3-b]pyridine-3-sulfonyl]}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrrolo[2,3-b]pyridine



Except for 6-[(1-methyl)-4-pyrazolyl]-1-H-pyrrolo[2,3-b]pyridine was used instead of 1-H-pyrazolo[3,4-b]pyridine, and 4-(4-methylpiperazine-1-carbonyl)phenylboronic acid was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound

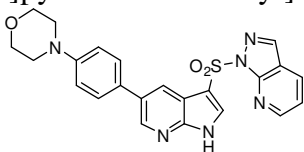
1-{{6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-1-H-pyrrolo[2,3-b]pyridine-3-sulfonyl}-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrrolo[2,3-b]pyridine was prepared by the same process as Example 107. ESI (m/z): 581.5 [M+H]<sup>+</sup>.

Example 109: Preparation of 1-[(3-chlorophenyl)-1-H-pyrrolo[2,3-b]pyridine-3-sulfonyl]-1-H-pyrazolo[3,4-b]pyridine



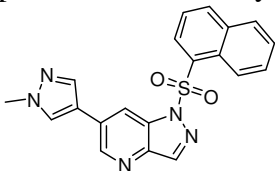
Except for 3-chlorophenylboronic acid was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(3-chlorophenyl)-1-H-pyrrolo[2,3-b]pyridine-3-sulfonyl]-1-H-pyrazolo[3,4-b]pyridine was prepared by the same process as Example 107. ESI (m/z): 410.0 [M+H]<sup>+</sup>.

Example 110: Preparation of 1-[(4-morpholinylphenyl)-1-H-pyrrolo[2,3-b]pyridine-3-sulfonyl]-1-H-pyrazolo[3,4-b]pyridine



Except for 4-morpholinylphenylboronic acid was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(3-chlorophenyl)-1-H-pyrrolo[2,3-b]pyridine-3-sulfonyl]-1-H-pyrazolo [3,4-b]pyridine was prepared by the same process as Example 107. ESI (m/z): 461.1 [M+H]<sup>+</sup>.

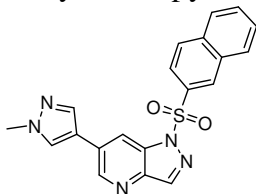
Example 111: Preparation of 1-(naphthalene-1-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for naphthalene-1-sulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(naphthalene-1-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 8.82 (t, *J* = 4.7 Hz, 2H), 8.53 (dd, *J* = 7.4, 1.0 Hz, 2H), 8.30 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.91 (m, 3H), 7.60 (m, 3H), 4.03 (s, 3H).

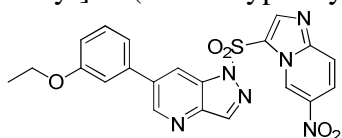
Example 112: Preparation of 1-(naphthalene-2-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for naphthalene-2-sulfonyl chloride was used instead of 2-nitrophenylsulfonyl chloride, compound 1-(naphthalene-2-sulfonyl)-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 3.

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.83 (d,  $J = 1.7$  Hz, 1H), 8.65 (s, 1H), 8.55 (s, 1H), 8.36 (s, 1H), 7.97 (m, 2H), 7.88 (m, 4H), 7.64 (m, 2H), 4.04 (s, 3H).

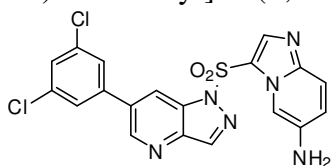
Example 113: Preparation of 1-[(6-nitro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3-ethoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 6-nitro-imidazo[1,2-a]pyridine-3-sulfonyl chloride was used instead of imidazo[1,2-a]pyridine-3-sulfonyl chloride, and 3-ethoxyphenylboronic acid was used instead of phenylboronic acid, compound 1-[(6-nitro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3-ethoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

$^1\text{H NMR}$  (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.83 (s, 1H), 9.11 (d,  $J = 6.3$  Hz, 2H), 8.89 (s, 1H), 8.59 (s, 1H), 8.12 – 8.05 (m, 1H), 7.77 (d,  $J = 9.5$  Hz, 1H), 7.56 – 7.48 (m, 2H), 7.40 (s, 1H), 7.13 – 7.07 (m, 1H), 4.22 – 4.10 (m, 2H), 1.39 (t,  $J = 7.1$  Hz, 3H).

Example 114: Preparation of 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3,5-dichlorophenyl)-1-H-pyrazolo[4,3-b]pyridine

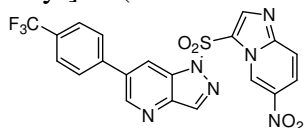


Except for 3,5-dichlorophenylboronic acid was used instead of 3-ethoxyphenylboronic acid, compound 1-[(6-nitro-imidazo[1,2-a]pyridine)

-3-sulfonyl]-6-(3,5-dichlorophenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 113. Eighty milligrams 1-[(6-nitro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3,5-dichlorophenyl)-1-H-pyrazolo[4,3-b]pyridine, 58 mg reduced iron powder and 28 mg ammonium formate were dissolved in toluene, reacted at 90°C for 8 hours, filtered while still hot, evaporated to remove the organic phase, the solid obtained from evaporation was dissolved in dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain compound 114 (m=42 mg, yield: 56%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.82 (s, 1H), 9.14 (d, J = 2.1 Hz, 1H), 9.11 (s, 1H), 8.92 (s, 1H), 8.67 (s, 1H), 8.08 (dd, J = 10.1, 2.5 Hz, 1H), 8.00 (d, J = 1.8 Hz, 2H), 7.82 – 7.79 (m, 1H), 7.77 (d, J = 9.9 Hz, 1H), 5.89 (br, 2H).

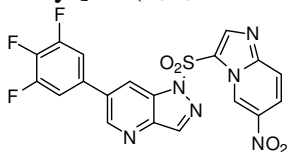
Example 115: Preparation of 1-[(6-nitro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-trifluoromethylphenyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 4-trifluoromethylphenylboronic acid was used instead of phenylboronic acid, compound 1-[(6-nitro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-trifluoromethylphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 113.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.82 (s, 1H), 9.18 (s, 1H), 9.10 (s, 1H), 8.92 (s, 1H), 8.69 (s, 1H), 8.25 – 8.17 (m, 2H), 8.07 (d, J = 11.5 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 10.0 Hz, 1H).

Example 116: Preparation of 1-[(6-nitro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3,4,5-trifluorophenyl)-1-H-pyrazolo[4,3-b]pyridine

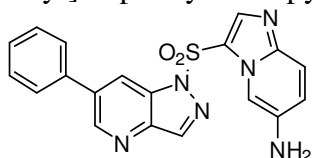


Except for 3,4,5-trifluorophenylboronic acid was used instead of phenylboronic acid, compound 1-[(6-nitro-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3,4,5-trifluorophenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process

as Example 113.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.82 (s, 1H), 9.12 (d,  $J$  = 6.0 Hz, 2H), 8.91 (s, 1H), 8.66 (s, 1H), 8.08 (d,  $J$  = 8.6 Hz, 1H), 8.03 – 7.92 (m, 2H), 7.77 (d,  $J$  = 12.2 Hz, 1H).

Example 117: Preparation of 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-phenyl-1-H-pyrazolo[4,3-b]pyridine



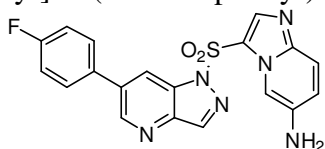
Except for phenylboronic acid was used instead of 3,5-dichlorophenylboronic acid, compound 1-[(6-amino-imidazo[1,2-a]pyridine)

-3-sulfonyl]-6-phenyl-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as

Example 114.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.86 (s, 1H), 9.14 (s, 1H), 9.12 (d,  $J$  = 2.0 Hz, 1H), 8.88 (s, 1H), 8.61 (s, 1H), 8.07 (dd,  $J$  = 10.0, 2.3 Hz, 1H), 7.88 (d,  $J$  = 7.1 Hz, 2H), 7.86 – 7.79 (m, 1H), 7.77 (d,  $J$  = 10.3 Hz, 1H), 7.57 – 7.50 (m, 2H), 5.39 (br, 2H).

Example 118: Preparation of 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-fluorophenyl)-1-H-pyrazolo[4,3-b]pyridine

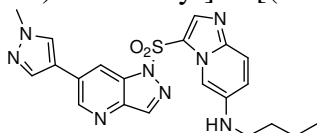


Except for 4-fluorophenylboronic acid was used instead of 3,5-dichlorophenylboronic acid, compound 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-fluorophenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by

the same process as Example 114.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.33 (s, 1H), 8.96 (d,  $J$  = 1.9 Hz, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.48 (s, 1H), 8.10 (dd,  $J$  = 10.0, 2.2 Hz, 1H), 7.76 – 7.67 (m, 3H), 7.30 (m, 2H), 6.09 (br, 2H).

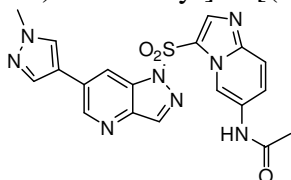
Example 119: Preparation of 1-[(6-n-butylamino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 1-methyl-1H-pyrazolo-4-borate pinacol ester was used instead of 3,5-dichlorophenylboronic acid, compound 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 114. Fifty milligrams 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine, 18 mg n-butylaldehyde, 32 mg sodium cyanoborohydride and 8  $\mu$ l acetic acid were dissolved in 30 ml methanol, reacted at 50°C for 8 hours, evaporated to remove the organic phase, the solid obtained by evaporation was dissolved in dichloromethane, washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain compound 119 (m=48 mg, yield: 85%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.86 (d, *J* = 1.9 Hz, 1H), 8.63 (dd, *J* = 2.0, 1.0 Hz, 1H), 8.38 (d, *J* = 1.0 Hz, 1H), 8.20 (s, 1H), 7.96 (d, *J* = 0.9 Hz, 1H), 7.88 (s, 1H), 7.33 (d, *J* = 9.7 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 6.81 (dd, *J* = 9.7, 2.2 Hz, 1H), 4.03 (s, 3H), 3.01 (t, *J* = 7.0 Hz, 2H), 1.66 (p, *J* = 7.2 Hz, 2H), 1.46 (h, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H).

Example 120: Preparation of 1-[(6-acetylamino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

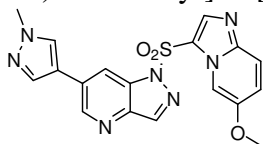


Except for 1-methyl-1H-pyrazolo-4-borate pinacol ester was used instead of 3,5-dichlorophenylboronic acid, compound 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 114. Fifty milligrams 1-[(6-amino-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine, 11 mg acetyl chloride and 18.5 mg 4-dimethylaminopyridine was dissolved in 30 ml dichloromethane, stirred at room temperature for 3 hours, the organic phase was washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography

to obtain compound 120 (m=53 mg, yield: 95%).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.24 (s, 1H), 9.34 (d,  $J = 1.9$  Hz, 1H), 9.06 (d,  $J = 1.9$  Hz, 1H), 9.03 (s, 1H), 8.71 (s, 1H), 8.54 (s, 1H), 8.48 (d,  $J = 1.4$  Hz, 1H), 8.17 (s, 1H), 7.55 (d,  $J = 9.8$  Hz, 1H), 7.28 (dd,  $J = 9.9, 2.0$  Hz, 1H), 3.93 (s, 3H), 2.08 (s, 3H).

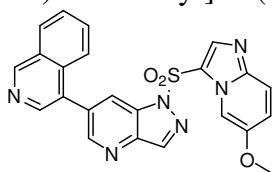
5            Example        121:            Preparation        of            1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine



10            Except for 6-methoxy-imidazo[1,2-a]pyridine-3-sulfonyl chloride was used instead of imidazo[1,2-a]pyridine-3-sulfonyl chloride, and 1-methyl-1H-pyrazolo-4-borate pinacol ester was used instead of phenylboronic acid, compound 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 28.

15             $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.85 (d,  $J = 1.9$  Hz, 1H), 8.65 – 8.62 (m, 1H), 8.44 (dd,  $J = 1.9, 0.9$  Hz, 1H), 8.33 (d,  $J = 0.9$  Hz, 1H), 8.23 (s, 1H), 7.93 (d,  $J = 0.9$  Hz, 1H), 7.85 (s, 1H), 7.59 (dd,  $J = 9.8, 0.7$  Hz, 1H), 7.55 (d,  $J = 0.8$  Hz, 1H), 7.43 (s, 1H), 7.25 (d,  $J = 2.4$  Hz, 1H), 4.03 (s, 3H), 3.95 (s, 3H).

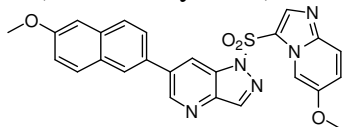
                 Example        122:            Preparation        of            1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-isoquinolinyl)-1-H-pyrazolo[4,3-b]pyridine



20            Except for isoquinoline-4-boronic acid was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-isoquinolinyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 121.

25             $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.40 (s, 1H), 8.87 (d,  $J = 1.7$  Hz, 1H), 8.68 (d,  $J = 2.1$  Hz, 1H), 8.64 (s, 1H), 8.57 (s, 1H), 8.49 (s, 1H), 8.23 (s, 1H), 8.14 (d,  $J = 7.9$  Hz, 1H), 7.78 (d,  $J = 3.5$  Hz, 2H), 7.77 – 7.70 (m, 1H), 7.61 (d,  $J = 9.7$  Hz, 1H), 7.33 – 7.28 (m, 1H), 3.97 (s, 3H).

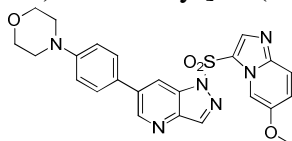
Example 123: Preparation of 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(6-methoxy-2-naphthyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 6-methoxynaphthalene-2-boronic acid was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(6-methoxy-2-naphthyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 121.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.06 (d, J = 1.9 Hz, 1H), 8.70 (dd, J = 1.9, 0.8 Hz, 1H), 8.66 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 0.8 Hz, 1H), 8.26 (s, 1H), 8.09 (d, J = 1.6 Hz, 1H), 7.90 (dd, J = 15.5, 8.8 Hz, 2H), 7.77 (dd, J = 8.5, 1.9 Hz, 1H), 7.59 (dd, J = 9.7, 0.6 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.24 – 7.20 (m, 1H), 3.98 (s, 3H), 3.94 (s, 3H).

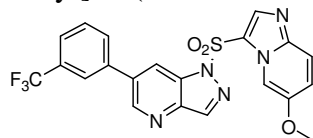
Example 124: Preparation of 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-morpholinylphenyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 4-morpholinylphenylboronic acid was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-morpholinylphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 121.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.92 (d, J = 1.9 Hz, 1H), 8.64 (dd, J = 2.5, 0.8 Hz, 1H), 8.54 (dd, J = 2.0, 0.9 Hz, 1H), 8.36 (d, J = 0.9 Hz, 1H), 8.23 (s, 1H), 7.66 – 7.61 (m, 2H), 7.58 (dd, J = 9.8, 0.8 Hz, 1H), 7.25 (dd, J = 9.8, 2.4 Hz, 1H), 7.09 – 7.02 (m, 2H), 3.94 (s, 3H), 3.93 – 3.88 (m, 4H), 3.31 – 3.25 (m, 4H).

Example 125: Preparation of 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3-trifluoromethylphenyl)-1-H-pyrazolo[4,3-b]pyridine

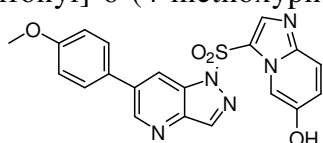


Except for 3-trifluoromethylphenylboronic acid was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound

1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3-trifluoromethylphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 121.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.94 (d, J = 1.9 Hz, 1H), 8.67 (d, J = 2.3 Hz, 1H), 8.64 – 8.60 (m, 1H), 8.43 (s, 1H), 8.25 (s, 1H), 7.92 (s, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.76 (s, 1H), 7.71 (t, J = 7.7 Hz, 1H), 7.60 (d, J = 9.7 Hz, 1H), 7.28 (dd, J = 9.7, 2.4 Hz, 1H), 3.97 (s, 3H).

Example 126: Preparation of 1-[(6-hydroxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-methoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine

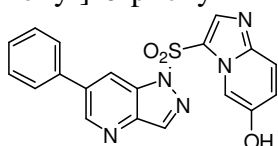


Except for 4-methoxyphenylboronic acid was used instead of 1-methyl-1H-pyrazolo-4-borate pinacol ester, compound 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(4-methoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 121. Fifty milligrams 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-

(4-methoxyphenyl)-1-H-pyrazolo[4,3-b]pyridine was dissolved in 20 ml dichloromethane, at 0°C, 33 µl boron tribromide was slowly and dropwisely added into the reactant liquid, stirred at room temperature for 3 hours after the addition was completed, the reactant liquid was cooled to 0°C again and 3 ml methanol was slowly added, then the organic phase was evaporated to dry, isolated by flash preparative chromatography to obtain compound 126 (m=16 mg, yield: 34%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.91 (d, J = 1.9 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H), 8.57 – 8.53 (m, 1H), 8.37 (s, 1H), 8.24 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 9.8 Hz, 1H), 7.26 (dd, J = 9.7, 2.4 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 3.94 (s, 3H).

Example 127: Preparation of 1-[(6-hydroxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-phenyl-1-H-pyrazolo[4,3-b]pyridine

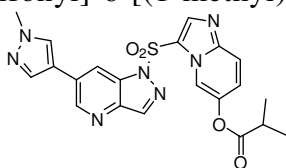


Except for phenylboronic acid was used instead of 4-methoxyphenylboronic acid, compound 1-[(6-hydroxy-imidazo[1,2-a]

pyridine)-3-sulfonyl]-6-phenyl-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 126.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.95 (d, *J* = 1.9 Hz, 1H), 8.65 (d, *J* = 2.2 Hz, 1H), 8.60 (d, *J* = 1.8 Hz, 1H), 8.40 (s, 1H), 8.24 (s, 1H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.62 – 7.47 (m, 4H), 7.27 (dd, *J* = 9.7, 2.4 Hz, 1H).

Example 128: Preparation of 1-[(6-isobutyryloxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

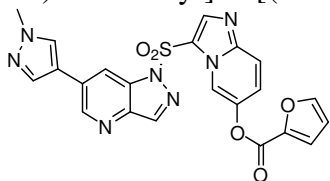


Compound 121 was used in the same process as Example 126 to produce 1-[(6-hydroxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine. Fifty milligrams

1-[(6-hydroxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine, 15 mg isobutyryl chloride and 18.5 mg 4-dimethylaminopyridine were dissolved in 30 ml dichloromethane, stirred at room temperature for 3 hours, the organic phase was washed three times with water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain compound 128 (m=54 mg, yield: 92%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.15 – 9.05 (m, 1H), 8.87 (d, *J* = 1.9 Hz, 1H), 8.46 (dd, *J* = 2.1, 1.1 Hz, 1H), 8.40 – 8.35 (m, 1H), 8.32 (s, 1H), 7.95 (d, *J* = 5.7 Hz, 1H), 7.88 (d, *J* = 6.2 Hz, 1H), 7.72 (d, *J* = 9.7 Hz, 1H), 7.41 – 7.32 (m, 1H), 4.04 (s, 3H), 2.90 (p, *J* = 6.9 Hz, 1H), 1.37 (dd, *J* = 7.1, 0.9 Hz, 6H).

Example 129: Preparation of 1-[(6-furan-2-acyloxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine

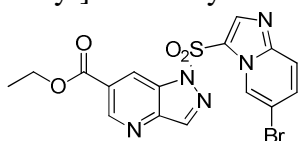


Except for 6-furan-2-carbonyl chloride was used instead of isobutyryl chloride, compound 1-[(6-furan-2-acyloxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the

same process as Example 128.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.31 – 9.20 (m, 1H), 8.94 – 8.83 (m, 1H), 8.52 – 8.45 (m, 1H), 8.41 (d,  $J$  = 0.9 Hz, 1H), 8.39 – 8.35 (m, 1H), 7.97 (d,  $J$  = 6.0 Hz, 1H), 7.90 (d,  $J$  = 8.4 Hz, 1H), 7.82 (d,  $J$  = 9.8 Hz, 1H), 7.78 (dt,  $J$  = 1.7, 0.9 Hz, 1H), 7.66 – 7.63 (m, 1H),  
5 7.56 – 7.50 (m, 2H), 4.06 (d,  $J$  = 0.9 Hz, 3H).

Example 130: Preparation of 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-ethoxycarbonyl-1-H-pyrazolo[4,3-b]pyridine



Three grams 6-bromopyrazolopyridine was dissolved in 80 ml anhydrous  
10 tetrahydrofuran, 3.6 ml n-butyl lithium was added at  $-78^\circ\text{C}$ , stirred for 5 minutes, 15 ml anhydrous tetrahydrofuran solution of ethyl chloroformate was added at  $-78^\circ\text{C}$ , further stirred for 30 minutes. The reaction was terminated by saturated sodium bicarbonate solution, ethyl acetate was added for extraction, the organic layer was evaporated to dry, isolated by flash preparative chromatography to obtain compound  
15 6-ethoxycarbonyl-1-H-pyrazolo[4,3-b]pyridine (m=200 mg, yield: 14%). ESI (m/z): 192.0  $[\text{M}+\text{H}]^+$ .

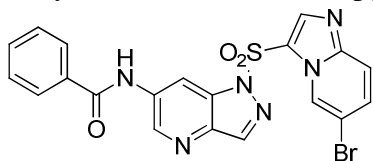
$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.02 (s, 1H), 8.53 (s, 1H), 8.45 (s, 1H), 4.39 (q,  $J$  = 7.1 Hz, 2H), 1.37 (t,  $J$  = 7.1 Hz, 3H).

Eighty milligrams sodium hydride and 53 mg ethyl pyrazolopyridine-6-formate were  
20 dissolved in 10 ml anhydrous tetrahydrofuran, stirred for 30 minutes, 60 mg 6-bromoimidazo[1,2-a]pyridine-3-sulfonyl chloride was dissolved in 10 ml anhydrous tetrahydrofuran, then slowly and dropwisely added into the reactant liquid, stirred at room temperature for 4 hours after the addition was completed. Tetrahydrofuran was removed by evaporation, the remainder was dissolved in dichloromethane, washed three times with  
25 water, the organic layer was dried over anhydrous sodium sulfate then concentrated, isolated by flash preparative chromatography to obtain compound 130 (m=15 mg, yield: 12%). ESI (m/z): 450.0  $[\text{M}+\text{H}]^+$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.35 (d,  $J$  = 1.6 Hz, 2H), 2 9.30 (s, 1H), 9.09 (s, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 7.67 (d,  $J$  = 9.6 Hz, 1H), 7.63 (t,  $J$  = 5.6 Hz, 1H), 4.55 (q,  $J$  =

7.1 Hz, 2H), 1.71 (s, 1H), 1.51 (t, J = 7.1 Hz, 3H).

Example 131: Preparation of 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-benzamido-1-H-pyrazolo[4,3-b]pyridine



5 6-bromo-1-H-pyrazolo[4,3-b]pyridine (1.07 g) was dissolved in 30 ml DMF, 0.72 g sodium hydride was added at 0°C, stirred for 30 minutes, 1.8 ml 2-(trisilyl)ethoxymethyl chloride was added, stirred at room temperature for 2 hours. Upon terminated with ice water, the reaction liquid was extracted with ethyl acetate, the organic phase was evaporated to dry, isolated by flash preparative chromatography to obtain compound  
10 1-[2-(trimethylsilyl)ethoxymethyl]-6-bromopyrazolo[4,3-b]pyridine (m=1.3 g, yield: 73.3%).

<sup>1</sup>H NMR (400 MHz, Acetone-*d*) δ 8.62 (s, 1H), 8.46 (s, 1H), 8.25 (s, 1H), 5.82 (s, 2H), 3.60 (t, J = 8.0 Hz, 2H), 0.86 (t, J = 8.0 Hz, 2H), -0.06 (d, J = 15.5 Hz, 9H).

Two hundred milligrams compound  
15 1-[2-(trimethylsilyl)ethoxymethyl]-6-bromopyrazolo[4,3-b]pyridine and 30 mg copper sulfate pentahydrate were dissolved in 5 ml concentrated aqueous ammonia, reacted overnight at 150°C in sealed vessel. The reactant liquid was extracted with ethyl acetate, the organic phase was evaporated to dry, isolated by flash preparative chromatography to obtain compound 1-[2-(trimethylsilyl)ethoxymethyl]-6-aminopyrazolo[4,3-b]pyridine  
20 (m=56 mg, yield: 34.8%).

<sup>1</sup>H NMR (400 MHz, Acetone-*d*) δ 8.14 (d, J = 2.3 Hz, 1H), 7.90 (s, 1H), 7.08 (d, J = 2.2 Hz, 1H), 5.59 (s, 2H), 3.54 (t, J = 8.0 Hz, 2H), 0.85 (t, J = 8.0 Hz, 2H), -0.07 (s, 9H).

One hundred milligrams compound 1-[2-(trisilyl)ethoxymethyl]-6-aminopyrazolo[4,3-b]pyridine was dissolved in 6 ml dichloromethane, 44 μl benzoyl  
25 chloride was added, stirred overnight at room temperature. The reactant liquid was extracted with ethyl acetate, the organic phase was evaporated to dry, isolated by flash preparative chromatography to obtain compound 1-[2-(trisilyl)ethoxymethyl]-6-benzoylamidopyrazolo[4,3-b]pyridine(m=116 mg, yield: 96%).

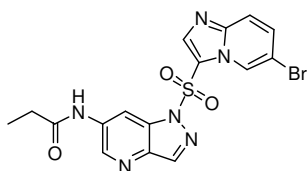
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.65 (d, J = 16.1 Hz, 2H), 8.34 (s, 1H), 8.20 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.54 (m, 3H), 5.73 (s, 2H), 3.70 – 3.56 (m, 2H), 1.00 – 0.89 (m, 2H), -0.03 (s, 9H).

One hundred and thirty-five milligrams compound  
5 1-[2-(trisilyl)ethoxymethyl]-6-benzoylamidopyrazolo[4,3-b]pyridine was added into 2 ml tetrahydrofuran solution of 1N TBAF, refluxed overnight. The reactant liquid was extracted with ethyl acetate, the organic layer was evaporated to dry, isolated by flash preparative chromatography to obtain compound  
6-benzamido-1H-pyrazolo[4,3-b]pyridine (m=40 mg, yield: 45.8%). ESI (m/z): 239.0  
10 [M+H]<sup>+</sup>.

Fourteen milligrams sodium hydride was suspended in 5 ml anhydrous tetrahydrofuran, 5 ml tetrahydrofuran solution comprising 40 mg compound 6-benzamido-1H-pyrazolo[4,3-b]pyridine was added, stirred for 30 minutes, 5 ml tetrahydrofuran solution comprising 50 mg compound  
15 6-bromoimidazo[1,2-a]pyridine-3-sulfonyl chloride was added, stirred at room temperature for 4 hours. Ethyl acetate was added for extraction, the organic layer was evaporated to dry, and purified by column chromatography, isolated by flash preparative chromatography to obtain compound 131 (m=50 mg, yield: 59.9%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.93 (s, 1H), 9.18 (s, 1H), 9.07 (s, 1H), 9.03 (s,  
20 1H), 8.77 (s, 1H), 8.48 (s, 1H), 8.06 (d, J = 7.7 Hz, 2H), 7.85 (s, 2H), 7.64 (m, 3H).

Example 132: Preparation of  
1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-propionamido-1-H-pyrazolo[4,3-b]pyr  
idine

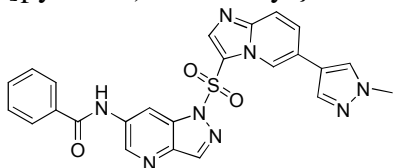


25 Except for propionyl chloride was used instead of benzoyl chloride, compound 1-[(6-bromo-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-propionamido-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 131.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.64 (s, 1H), 9.05 (d, J = 1.1 Hz, 1H), 9.00 (s, 1H), 8.75 (d, J = 1.8 Hz, 1H), 8.72 (s, 1H), 8.44 (s, 1H), 7.84 (s, 2H), 2.49 – 2.42 (q, 2H),

1.14 (t, J = 7.5 Hz, 3H).

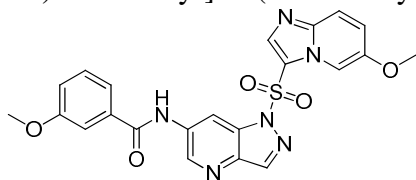
Example 133: Preparation of 1-[(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-benzamido-1-H-pyrazolo[4,3-b]pyridine



5 Into a microwave reaction tube were disposed 40 mg compound 131, 20 mg 1-methyl-1H-pyrazolo-4-borate pinacol ester and 33 mg potassium carbonate, 5 ml dioxane, 2.5 ml ethanol and 2.5 ml water were added into the microwave reaction tube, air was displaced for three times, under a nitrogen atmosphere, 3.2 mg complex of 1,1'-bis(diphenylphosphino) ferrocene palladium (II) dichloride and dichloromethane was added into the microwave tube, then the microwave tube was sealed. The microwave tube was placed into a microwave reactor, reaction was conducted at a temperature of 120°C for 30 minutes, the reaction was completed. The aforementioned reactant liquid was poured into 15 ml water, extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate then concentrated. The concentrated solid was dissolved into 10 ml dioxane saturated with hydrochloric acid, stirred at room temperature for 3 hours, evaporated to remove the organic phase, and isolated by flash preparative chromatography to obtain the target compound 133 (m=20 mg, yield: 50%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.03 (s, 1H), 9.29 (s, 1H), 9.07 (s, 1H), 8.90 (s, 1H), 8.74 (s, 1H), 8.47 (s, 1H), 8.25 (s, 1H), 8.09 (d, J = 7.8 Hz, 2H), 7.90 (d, J = 7.1 Hz, 2H), 7.73 – 7.54 (m, 3H), 3.86 (s, 3H).

Example 134: Preparation of 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3-methoxybenzamido)-1-H-pyrazolo[4,3-b]pyridine

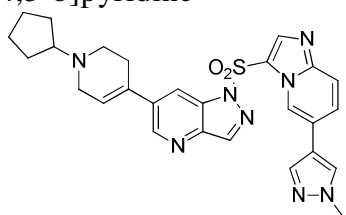


Except for 3-methoxybenzoyl chloride was used instead of benzoyl chloride, and 6-methoxyimidazo[1,2-a]pyridine-3-sulfonyl chloride was used instead of 6-bromoimidazo[1,2-a]pyridine-3-sulfonyl chloride, compound 1-[(6-methoxy-imidazo[1,2-a]pyridine)-3-sulfonyl]-6-(3-methoxybenzamido)-1-H-pyrazol

o[4,3-b]pyridine was prepared by the same process as Example 131.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.46 (s, 1H), 8.35 (dd, *J* = 9.4, 1.9 Hz, 2H), 8.26 (d, *J* = 1.9 Hz, 1H), 7.87 (s, 1H), 7.63 – 7.38 (m, 4H), 7.27 – 7.10 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H).

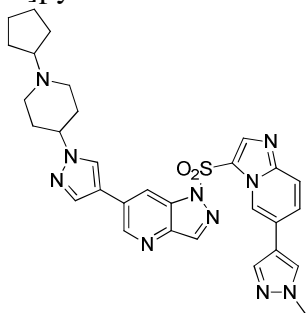
5        Example 135: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-cyclopentyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine



10        Except for 1-cyclopentyl-1,2,3,6-tetrahydropyridine-4-borate pinacol ester was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-cyclopentyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

15        <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.15 (s, 1H), 8.78 (d, *J* = 1.6 Hz, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.28 (s, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.67 – 7.60 (m, 1H), 6.29 (m, 1H), 4.03 (s, 3H), 3.67 (m, 2H), 3.21 (m, 2H), 3.12 (m, 1H), 2.95 (m, 2H), 2.08 (m, 2H), 1.89 (m, 4H), 1.65 (m, 2H).

20        Example 136: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{{1-[(1-cyclopentyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine

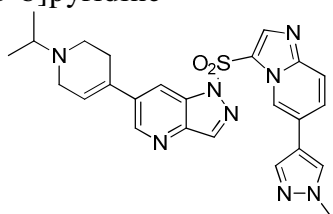


Except for 1-[(1-cyclopentyl)-4-piperidinyl]pyrazolo-4-borate pinacol ester was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]

pyridine)-3-sulfonyl}-6-{1-[(1-cyclopentyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.16 (s, 1H), 8.85 (d, *J* = 1.8 Hz, 1H), 8.50 – 8.44 (m, 1H), 8.34 (s, 1H), 8.30 (s, 1H), 8.00 (s, 1H), 7.94 (s, 1H), 7.80 (s, 1H), 7.76 (s, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.63 (dd, *J* = 9.3, 1.7 Hz, 1H), 4.59 – 4.46 (m, 1H), 4.01 (s, 3H), 3.55 (q, *J* = 10.0 Hz, 2H), 3.14 (dd, *J* = 21.5, 6.8 Hz, 1H), 2.53 – 2.42 (m, 2H), 2.06 (dt, *J* = 13.3, 7.1 Hz, 3H), 2.00 – 1.81 (m, 6H), 1.64 (dd, *J* = 12.8, 4.8 Hz, 3H).

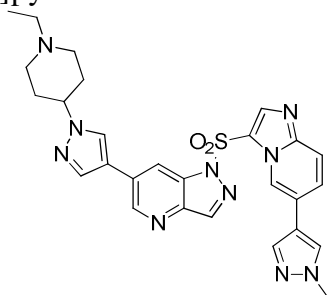
Example 137: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-isopropyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine



Except for 1-isopropyl-1,2,3,6-tetrahydropyridine-4-borate pinacol ester was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[(1-isopropyl)-4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.14 (s, 1H), 8.77 (d, *J* = 1.8 Hz, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 8.30 (s, 1H), 7.80 (s, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 9.4 Hz, 1H), 7.63 (dd, *J* = 9.3, 1.7 Hz, 1H), 6.30 (m, 1H), 4.02 (s, 3H), 3.75 – 3.68 (m, 2H), 3.37 (m, 1H), 3.25 (m, 2H), 3.01 (m, 2H), 1.41 (d, *J* = 6.6 Hz, 6H).

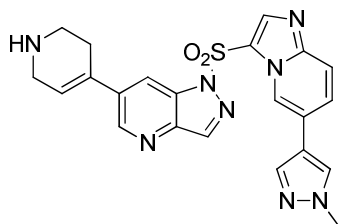
Example 138: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{1-[(1-ethyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine



Except for 1-[(1-ethyl)-4-piperidinyl]pyrazolo-4-borate pinacol ester was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{[1-[(1-ethyl)-4-piperidinyl]]-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.05 (d, *J* = 1.8 Hz, 1H), 8.96 (s, 1H), 8.75 (s, 1H), 8.65 (s, 1H), 8.60 (s, 2H), 8.36 (s, 1H), 8.27 (s, 1H), 7.96 (d, *J* = 13.6 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 1H), 4.82 (d, *J* = 13.6 Hz, 1H), 4.52 - 4.40 (m, 1H), 4.03 (d, *J* = 13.6 Hz, 1H), 3.36 - 3.25 (m, 1H), 2.81 (dd, *J* = 18.6, 7.3 Hz, 1H), 2.29 (dd, *J* = 24.4, 12.2 Hz, 2H), 2.18 (m, 2H), 2.13 - 1.96 (m, 2H), 1.35 (t, *J* = 6.6 Hz, 3H).

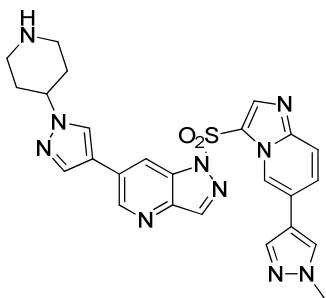
Example 139: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine



Except for 1,2,3,6-tetrahydropyridine-4-borate pinacol ester was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-[4-(1,2,3,6-tetrahydropyridinyl)]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.15 (s, 1H), 8.78 (s, 1H), 8.36 (s, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.71 (d, *J* = 9.3 Hz, 1H), 7.62 (d, *J* = 9.6 Hz, 1H), 6.39 (m, 1H), 4.02 (s, 3H), 3.70 - 3.60 (m, 2H), 3.21 (t, *J* = 5.6 Hz, 2H), 2.65 - 2.53 (m, 2H).

Example 140: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{[1-(4-piperidinyl)]-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine

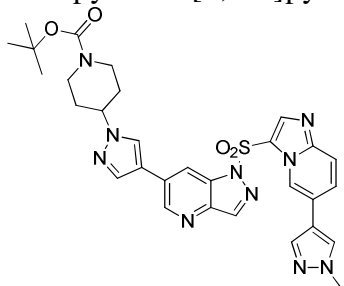


Except for 1-(4-piperidinyl)-pyrazolo-4-borate pinacol ester was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}

5 -6-{[1-(4-piperidinyl)]-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.05 (d, *J* = 1.8 Hz, 1H), 8.96 (s, 1H), 8.75 (s, 1H), 8.65 (s, 1H), 8.60 (s, 2H), 8.36 (s, 1H), 8.27 (s, 1H), 7.96 (d, *J* = 13.6 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 1H), 4.51 (m, 2H), 3.95 (s, 3H), 3.40 (m, 3H), 3.06 (m, 3H).

10 Example 141: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{[1-(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine

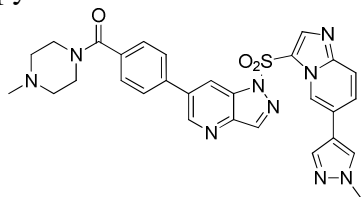


15 Except for 1-[(1-t-butoxycarbonyl)-4-piperidinyl]-pyrazolo-4-borate pinacol ester was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo[1,2-a]pyridine)-3-sulfonyl}-6-{[1-(1-t-butoxycarbonyl)-4-piperidinyl]}-4-pyrazolyl}-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

20 <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 9.17 (s, 1H), 8.86 (d, *J* = 1.9 Hz, 1H), 8.46 (m, 1H), 8.33 (s, 1H), 8.28 (s, 1H), 7.95 (s, 1H), 7.87 (s, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.72 (d, *J* = 9.4 Hz, 1H), 7.63 (dd, *J* = 9.3, 1.7 Hz, 1H), 4.35 (m, 3H), 4.04 (s, 3H), 2.95 (m, 2H), 2.20 (m, 2H), 2.00 (m, 4.4 Hz, 2H), 1.50 (s, 9H).

Example 142: Preparation of 1-{(6-[(1-methyl)-4-pyrazolyl]-imidazo

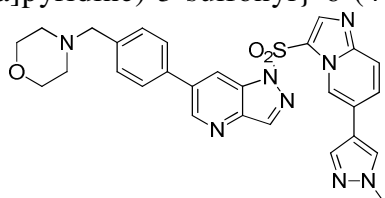
[1,2-a]pyridine)-3-sulfonyl}-6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-1-H-pyrazolo[4,3-b]pyridine



Except for 4-(4-methylpiperazine-1-carbonyl)phenylborate was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-((6-((1-methyl)-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-[4-(4-methylpiperazine-1-carbonyl)phenyl]-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.19 (s, 1H), 8.94 (d, *J* = 1.8 Hz, 1H), 8.65 – 8.59 (m, 1H), 8.41 (s, 1H), 8.29 (s, 1H), 7.83 (s, 1H), 7.77 – 7.70 (m, 4H), 7.67 – 7.58 (m, 3H), 4.01 (s, 3H), 3.94 – 3.80 (m, 2H), 3.61 – 3.45 (m, 2H), 2.62 – 2.50 (m, 2H), 2.48 – 2.39 (m, 2H), 2.36 (s, 3H).

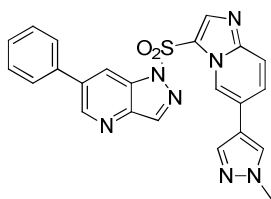
Example 143: Preparation of 1-((6-((1-methyl)-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-(4-morpholinomethylphenyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 4-morpholinomethylphenylboronic acid was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-((6-((1-methyl)-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-(4-morpholinomethylphenyl)-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.18 (s, 1H), 8.94 (s, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 8.29 (s, 1H), 7.82 (s, 1H), 7.75 (s, 1H), 7.72 (d, *J* = 9.3 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 3H), 7.53 (d, *J* = 7.9 Hz, 2H), 4.01 (s, 3H), 3.76 (t, *J* = 4.6 Hz, 4H), 3.60 (s, 2H), 2.59 – 2.44 (m, 4H).

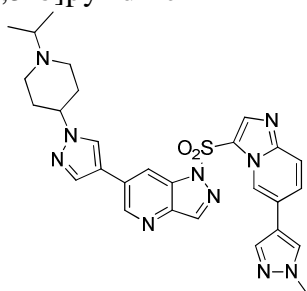
Example 144: Preparation of 1-((6-((1-methyl)-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-phenyl-1-H-pyrazolo[4,3-b]pyridine



Except for phenylboronic acid was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-((6-((1-methyl)-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-phenyl-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.18 (s, 1H), 8.95 (s, 1H), 8.62 (s, 1H), 8.40 (s, 1H), 8.30 (s, 1H), 7.82 (s, 1H), 7.76 – 7.67 (m, 4H), 7.63 (d,  $J$  = 9.3 Hz, 1H), 7.57 (t,  $J$  = 7.4 Hz, 2H), 7.51 (t,  $J$  = 7.2 Hz, 1H), 4.00 (s, 3H).

Example 145: Preparation of 1-((6-((1-methyl)-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-((1-(1-isopropyl)-4-piperidinyl)-4-pyrazolyl)-1-H-pyrazolo[4,3-b]pyridine



Except for 1-[(1-isopropyl)-4-piperidinyl]pyrazolo-4-borate pinacol ester was used instead of 1-t-butoxycarbonyl-1H-pyrazolo-4-borate pinacol ester, compound 1-((6-((1-methyl)-4-pyrazolyl)-imidazo[1,2-a]pyridine)-3-sulfonyl)-6-phenyl-1-H-pyrazolo[4,3-b]pyridine was prepared by the same process as Example 106.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.16 (s, 1H), 8.85 (s, 1H), 8.46 (s, 1H), 8.33 (s, 1H), 8.29 (s, 1H), 7.94 (d,  $J$  = 6.8 Hz, 2H), 7.81 (s, 1H), 7.74 (s, 1H), 7.72 (d,  $J$  = 9.3 Hz, 1H), 7.63 (d,  $J$  = 9.4 Hz, 1H), 4.27 (td,  $J$  = 10.9, 5.4 Hz, 1H), 4.00 (s, 3H), 3.12 (dd,  $J$  = 9.7, 6.1 Hz, 2H), 2.91 (p,  $J$  = 6.6 Hz, 1H), 2.46 (t,  $J$  = 11.5 Hz, 2H), 2.40 – 2.28 (m, 2H), 2.23 – 2.01 (m, 2H), 1.14 (d,  $J$  = 6.5 Hz, 6H).

### Test I: The effect of compounds on c-Met enzyme activity at the molecular level

## 1. Test method

Enzymatic reaction substrate Poly(Glu,Tyr)4:1 was diluted to 20 µg/mL in potassium ion free PBS (10 mM sodium phosphate buffer, 150 mM NaCl, pH7.2-7.4), microplate was coated with this solution at 125 µL per well, and reacted at 37°C for 12-16 hours. Liquid in wells was discarded. Plate washing: the plate was washed 3 times for 5 minutes each with 200 µL per well of T-PBS (potassium ion free PBS containing 0.1% Tween-20). The microplate was dried in 37°C oven for 1-2 hours.

Into each well was added 49µL diluted ATP solution in reaction buffer (50 mM HEPES pH 7.4, 50 mM MgCl<sub>2</sub>, 0.5 mM MnCl<sub>2</sub>, 0.2 mM Na<sub>3</sub>VO<sub>4</sub>, 1 mM DTT), and 1 µL per well of compound to be tested was added, then 50 µL diluted solution of c-Met kinase domain recombinant protein in reaction buffer was added to initiate the reaction, each test was setup with two wells of ATP free control. Reaction was performed in a 37°C shaker (100 rpm) for 1 hour. Liquid in the wells was discarded, and the plate was washed three times with T-PBS.

Antibody PY99 was added at 100 µL per well (the antibody was 1:500 diluted in T-PBS containing 5mg/mL BSA), incubated in a 37°C shaker for 0.5 hour. Liquid in the wells was discarded, and the plate was washed three times with T-PBS.

Goat anti mouse secondary antibody labeled with horseradish peroxidase was added at 100 µL per well (the antibody was 1:2000 diluted in T-PBS containing 5mg/mL BSA), incubated in a 37°C shaker for 0.5 hour. Liquid in the wells was discarded, and the plate was washed three times with T-PBS.

OPD visualization solution (2 mg/ml) was added at 100 µL per well (diluted in 0.1 M citric acid – sodium citrate buffer containing 0.03% H<sub>2</sub>O<sub>2</sub> (pH=5.4)), reacted in dark at 25°C for 1-10 minutes.

Reaction was terminated by adding 50µL per well of 2M H<sub>2</sub>SO<sub>4</sub>, the plate was read at 490nm using a VERSAmax microplate reader with tunable wavelength.

Inhibition rate of the sample was calculated using the following equation:

$$\text{Inhibition rate of sample (\%)} = \left(1 - \frac{\text{OD of compound} - \text{OD of enzyme free control}}{\text{OD of negative control} - \text{OD of enzyme free control}}\right) \times 100$$

## 2. Test result

The enzyme activity test at the molecular level (Table 1) suggests that the compounds of this invention can significantly inhibit c-Met tyrosine kinase activity, some of the compounds exhibited c-Met inhibition activity stronger than the comparative compound 1-(benzo[1,2,5]oxadiazole-4-sulfonyl)

5 -6-[(1-methyl)-4-pyrazolyl]-1-H-pyrazolo[4,3-b]pyridine (an analogue reported in Bioorganic & Medicinal Chemistry Letters 19 (2009) 2780-2784), but weaker than the activity of the positive control PF2341066.

**Table 1 Receptor tyrosin kinase c-Met inhibition rate by compounds at a concentration of 10  $\mu$ M**

| Compound No. | Inhibition rate at 10 $\mu$ M (%) | Compound No. | Inhibition rate at 10 $\mu$ M (%) |
|--------------|-----------------------------------|--------------|-----------------------------------|
| 1            | 88.1                              | 2            | 92.8                              |
| 3            | 84.6                              | 4            | 44.1                              |
| 5            | 57.5                              | 6            | 34.4                              |
| 7            | 40.7                              | 8            | 72.4                              |
| 9            | 22                                | 10           | 37.9                              |
| 11           | 48.6                              | 12           | 37.5                              |
| 13           | 52.6                              | 14           | 74.3                              |
| 15           | 40.6                              | 16           | 73.2                              |
| 17           | 49.9                              | 18           | 64                                |
| 19           | 59.3                              | 20           | 85.7                              |
| 21           | 77.9                              | 22           | 69.5                              |
| 23           | 65.1                              | 24           | 70.5                              |
| 25           | 86.2                              | 26           | 65.2                              |
| 27           | 70.6                              | 28           | 70.6                              |
| 29           | 65.7                              | 30           | 71                                |
| 31           | 69                                | 32           | 64.2                              |
| 33           | 53.7                              | 34           | 61.3                              |
| 35           | 62.5                              | 36           | 66.3                              |

|    |       |    |       |
|----|-------|----|-------|
| 37 | 73.3  | 38 | 87.1  |
| 39 | 68.8  | 40 | 66    |
| 41 | 68.7  | 42 | 67.5  |
| 43 | 58.4  | 44 | 87.5  |
| 45 | 89.6  | 46 | 81.3  |
| 47 | 79.8  | 48 | 87.3  |
| 49 | 76.7  | 50 | 93.9  |
| 51 | 72.3  | 52 | 54.5  |
| 53 | 65.7  | 54 | 70.7  |
| 55 | 74.1  | 56 | 62.1  |
| 57 | 60.8  | 58 | 58.9  |
| 59 | 60.3  | 60 | 57.4  |
| 61 | 59.8  | 62 | 62.6  |
| 63 | 83.2  | 64 | 80    |
| 65 | 79.3  | 66 | 63    |
| 67 | 66    | 68 | 69.8  |
| 69 | 79.9  | 70 | 68.2  |
| 71 | 62    | 72 | 80.9  |
| 73 | 59.6  | 74 | >67.6 |
| 75 | >77.3 | 76 | >76.3 |
| 77 | >76.9 | 78 | >12.1 |
| 79 | >83.1 | 80 | >75.3 |
| 81 | >68.7 | 82 | >78.5 |
| 83 | >79.8 | 84 | >71.5 |
| 85 | >71.2 | 86 | >67.9 |
| 87 | >76.8 | 88 | >70.2 |
| 89 | >71.7 | 90 | >72.2 |

|     |       |     |       |
|-----|-------|-----|-------|
| 91  | >69.4 | 92  | >71.9 |
| 93  | >64.5 | 94  | >74.3 |
| 95  | >72.1 | 96  | >71.8 |
| 97  | >63.8 | 98  | >77.9 |
| 99  | >73.3 | 100 | >60.4 |
| 101 | >64.5 | 102 | >65.5 |

## **Test II: Additional test on the effect of compounds on c-Met enzyme activity at the molecular level**

### **1. Test method**

5 Enzymatic reaction substrate Poly(Glu,Tyr)<sub>4:1</sub> was diluted to 20 µg/mL in potassium ion free PBS (10 mM sodium phosphate buffer, 150 mM NaCl, pH7.2-7.4), microplate was coated with this solution at 125 µL per well, and reacted at 37°C for 12-16 hours. Liquid in wells was discarded, then the plate was washed 3 times for 5 minutes each with 200 µL per well of T-PBS (PBS containing 0.1% Tween-20). The microplate was dried in  
10 37°C oven for 1-2 hours.

Into each well was added 50 µL diluted ATP solution in reaction buffer (50 mM HEPES pH 7.4, 50 mM MgCl<sub>2</sub>, 0.5 mM MnCl<sub>2</sub>, 0.2 mM Na<sub>3</sub>VO<sub>4</sub>, 1 mM DTT), the final concentration was 5 µM. Test compound was diluted in DMSO to proper concentration, added at 1 µL per well or corresponding level of DMSO (negative control wells), then 49  
15 µL diluted solution of c-Met kinase domain recombinant protein in reaction buffer was added to initiate the reaction, each test was setup with two wells of ATP free control. Reaction was performed in a 37°C shaker (100 rpm) for 1 hour. The plate was washed three times with T-PBS. Primary antibody PY99 diluted solution was added at 100 µL per well, incubated in a 37°C shaker for 0.5 hour. The plate was washed three times with  
20 T-PBS. Goat anti mouse secondary antibody labeled with horseradish peroxidase was added at 100 µL per well, incubated in a 37°C shaker for 0.5 hour. The plate was washed three times with T-PBS. OPD visualization solution (2 mg/ml) was added at 100 µL per well (diluted in 0.1 M citric acid – sodium citrate buffer containing 0.03% H<sub>2</sub>O<sub>2</sub> (pH=5.4)), reacted in dark at 25°C for 1-10 minutes (OPD dissolve was accomplished with ultrasound

treatment, and the visualization solution was made immediately prior to use). Reaction was terminated by adding 50 µL per well of 2M H<sub>2</sub>SO<sub>4</sub>, the plate was read at 490 nm using a SPECTRA MAX 190 microplate reader with tunable wavelength.

Inhibition rate of the sample was calculated using the following equation:

5      Inhibition rate (%) =  $(1 - \frac{\text{OD of compound} - \text{OD of ATP free control}}{\text{OD of negative control} - \text{OD of ATP free control}}) \times 100$

IC<sub>50</sub> was calculated by fitting the data for a four parameter fit using inhibition curve.

Test results are shown below in Table 2.

### 10      **Test III: Test about the effect of compounds on c-Met mediated proliferation of tumor cell and engineered cell proliferation**

#### 1. Test method

Assays on the growth inhibition of the compounds against gastric tumor cell MKN45, non-small cell carcinoma EBC-1 cell (both are MET persistent activated cell lines due to *MET* gene amplification, and are Met dependent tumor cell lines, MKN45 cell was purchased from JCRB, Japan, EBC-1 cell was purchased from ATCC, USA) were detected using sulforhodamine B (SRB) staining. A certain amount of MKN45 cells and EBC-1 cells at log phase were inoculated into 96-well culture plate at 90 µL per well, incubated overnight and then 10 µL compound at various concentrations or vehicle control (normal saline) was added, each concentration was tested in triplicate. After incubation with compound for 72 hours, the incubation was terminated, adherent cells were retained and medium was discarded, 10% (w/v) trichloroacetic acid (100 µL pre well) was added, the cells were fixed at 4°C for 1 hour, then rinsed with distilled water for 5 times, after dried at room temperature, SRB solution (4 mg/mL, dissolved in 1% glacial acetic acid) was added at 100 µL per well, incubated and stained at room temperature for 15 minutes, then rinsed with 1% glacial acetic acid for 5 times to remove any unbound SRB, dried at room temperature, then 10 mM Tris solution was added at 100 µL per well, the optical density (OD) value at 515 nm was measured using VERSMax microplate reader.

The inhibition rate of tumor cell growth by the compound was calculated by the following equation: inhibition rate (%) = (OD of control well - OD of administered well) / OD of control well × 100%. Experiments were conducted in duplicates. IC<sub>50</sub> value was

calculated by fitting the data for a four parameter fit using inhibition curve, the results are shown below in Table 2.

Assays on the growth inhibition of the compounds against engineered BaF3/TPR-Met cell (engineered cell line having TPR-Met fusion protein stably expressed in cytoplasm, persistently activated, Met dependent sensitive cell line; BaF3 cell was purchased from DSMZ, German) were detected using microculture tetrazolium (MTT) staining. A certain amount of BaF3/TPR-Met cells at log phase were inoculated into 96-well culture plate at 90  $\mu$ L per well, incubated overnight and then 10  $\mu$ L compound at various concentrations or vehicle control (normal saline) was added, each concentration was tested in triplicate. After incubation with compound for 72 hours, the incubation was terminated, MTT solution (5 mg/mL) was added at 20  $\mu$ L per well, incubated at 37°C for 4 hours, then 100  $\mu$ L triplet solution (10% SDS - 5% isobutanol - 0.01 M HCl) was added, incubated overnight at 37°C, OD value was measured at 570 nm. The inhibition rate of tumor cell growth by the compound was calculated by the following equation: inhibition rate (%) = (OD of control well - OD of administered well) / OD of control well  $\times$  100%. Experiments were conducted in duplicates. The results are shown below in Table 2.

**Table 2**

| Compound | Average inhibition rate at 10 $\mu$ M (%) | Average inhibition rate at 1 $\mu$ M (%) | Average inhibition rate at 0.1 $\mu$ M (%) | IC50 (nM)     | Cell proliferation inhibition rate at 1 $\mu$ M (%) | Cell proliferation inhibition rate at 200 nM (%) | Cell line    |
|----------|-------------------------------------------|------------------------------------------|--------------------------------------------|---------------|-----------------------------------------------------|--------------------------------------------------|--------------|
| 01       | 88.1                                      |                                          |                                            |               |                                                     |                                                  |              |
| 02       | 92.8                                      | 7                                        |                                            |               |                                                     |                                                  |              |
| 03       | 84.6                                      |                                          |                                            |               |                                                     |                                                  |              |
| 04       | 44.1                                      |                                          |                                            |               |                                                     |                                                  |              |
| 05       | 57.5                                      | 33.8                                     | 2.1                                        |               |                                                     |                                                  |              |
| 06       | 34.4                                      |                                          |                                            |               |                                                     |                                                  |              |
| 07       | 40.7                                      |                                          |                                            |               |                                                     |                                                  |              |
| 08       | 72.4                                      | 51.6                                     | 9.2                                        |               |                                                     |                                                  |              |
| 09       | 22                                        |                                          |                                            |               |                                                     |                                                  |              |
| 10       | 37.9                                      |                                          |                                            |               |                                                     |                                                  |              |
| 11       | 48.6                                      |                                          |                                            |               |                                                     |                                                  |              |
| 12       | 37.5                                      |                                          |                                            |               |                                                     |                                                  |              |
| 13       | 52.6                                      | 45.3                                     | 28.5                                       |               |                                                     |                                                  |              |
| 14       | 74.3                                      | 54.7                                     | 39.9                                       |               |                                                     |                                                  |              |
| 15       | 40.6                                      |                                          |                                            |               |                                                     |                                                  |              |
| 16       | 73.2                                      | 56.1                                     | 25.2                                       |               |                                                     |                                                  |              |
| 17       | 49.9                                      |                                          |                                            |               |                                                     |                                                  |              |
| 18       | 64                                        | 60.5                                     | 52.2                                       | 4.2 $\pm$ 0.6 | 94.4                                                | 1.8                                              | BaF3/TPR-Met |

| Compound | Average inhibition rate at 10 $\mu$ M (%) | Average inhibition rate at 1 $\mu$ M (%) | Average inhibition rate at 0.1 $\mu$ M (%) | IC50 (nM)         | Cell proliferation inhibition rate at 1 $\mu$ M (%) | Cell proliferation inhibition rate at 200 nM (%) | Cell line    |
|----------|-------------------------------------------|------------------------------------------|--------------------------------------------|-------------------|-----------------------------------------------------|--------------------------------------------------|--------------|
| 19       | 59.3                                      | 53.5                                     | 59.2                                       | 7.8 $\pm$ 0.8     | 95.6                                                | 91.8                                             | BaF3/TPR-Met |
| 20       | 85.7                                      | 72.6                                     | 54.9                                       | 316.2 $\pm$ 141.5 | 2.9                                                 | 3.2                                              | BaF3/TPR-Met |
| 21       | 77.9                                      | 59.7                                     | 59                                         |                   | 42.7                                                |                                                  | BaF3/TPR-Met |
| 22       | 69.5                                      | 58.7                                     | 24.9                                       | 39.7 $\pm$ 6.3    |                                                     |                                                  |              |
| 23       | 65.1                                      | 52.7                                     | 26.9                                       | 3.7 $\pm$ 1.4     |                                                     |                                                  |              |
| 24       | 70.5                                      | 67.8                                     | 62.9                                       | 2.5 $\pm$ 1.2     | 90.9                                                | 65.9                                             | BaF3/TPR-Met |
| 25       | 86.2                                      | 78                                       | 71.7                                       | 21.3 $\pm$ 2.3    | 88.4                                                | 36.3                                             | BaF3/TPR-Met |
| 26       | 65.2                                      | 63.8                                     | 60                                         | 33.9 $\pm$ 6.9    |                                                     |                                                  | BaF3/TPR-Met |
| 27       | 70.6                                      | 59.6                                     | 56.9                                       | 0.5 $\pm$ 0.1     |                                                     |                                                  | EBC-1        |
| 28       | 70.6                                      | 70.3                                     | 64.6                                       | 6.7 $\pm$ 0.5     | 66.1                                                |                                                  | BaF3/TPR-Met |
| 29       | 65.7                                      | 63.8                                     | 55.7                                       | 4.6 $\pm$ 1.0     | 92.6                                                |                                                  | BaF3/TPR-Met |
| 30       | 71                                        | 59.7                                     | 48.3                                       |                   |                                                     |                                                  |              |
| 31       | 69                                        | 64.1                                     | 59                                         |                   |                                                     |                                                  |              |
| 32       | 64.2                                      | 52                                       | 52.9                                       |                   |                                                     |                                                  |              |
| 33       | 53.7                                      | 47.3                                     | 39.9                                       |                   |                                                     |                                                  |              |
| 34       | 61.3                                      | 49.3                                     | 31.3                                       |                   |                                                     |                                                  |              |
| 35       | 62.5                                      | 53.2                                     | 51.1                                       |                   |                                                     |                                                  |              |
| 36       | 66.3                                      | 60                                       | 45.6                                       |                   |                                                     |                                                  |              |
| 37       | 73.3                                      | 63.8                                     | 60.1                                       | 6.4 $\pm$ 2.2     | 96.2                                                | 59.5                                             | BaF3/TPR-Met |
| 38       | 87.1                                      | 63.9                                     | 63.2                                       |                   |                                                     |                                                  |              |
| 39       | 68.8                                      | 65                                       | 58.2                                       | 2.6 $\pm$ 0.3     | 96.3                                                | 74.4                                             | BaF3/TPR-Met |
| 40       | 66                                        | 57.4                                     | 45.7                                       |                   |                                                     |                                                  |              |
| 41       | 68.7                                      | 54.6                                     | 45.1                                       |                   |                                                     |                                                  |              |
| 42       | 67.5                                      | 58.4                                     | 45.5                                       |                   |                                                     |                                                  |              |
| 43       | 68.7                                      | 47.6                                     | 23.1                                       |                   |                                                     |                                                  |              |
| 44       | 87.5                                      | 78.6                                     | 74.6                                       | 6.9 $\pm$ 1.9     | 95.8                                                | 95                                               | BaF3/TPR-Met |
| 45       | 89.6                                      | 76.5                                     | 73.4                                       | 2.9 $\pm$ 0.6     | 95.9                                                | 27.9                                             | BaF3/TPR-Met |
| 46       | 81.3                                      | 65                                       | 55.9                                       |                   | 68                                                  | 33.7                                             | BaF3/TPR-Met |
| 47       | 79.8                                      | 56.1                                     | 35.1                                       |                   |                                                     |                                                  |              |
| 48       | 87.3                                      | 77.6                                     | 65.6                                       |                   |                                                     |                                                  |              |
| 49       | 76.7                                      | 74.5                                     | 71                                         |                   | 90.5                                                | 28.4                                             | BaF3/TPR-Met |
| 50       | 93.9                                      | 67.4                                     | 66.8                                       |                   | 30.5                                                | 32.7                                             | BaF3/TPR-Met |
| 51       | 72.3                                      | 66.7                                     | 64.6                                       |                   | 7.7                                                 | 15.3                                             | BaF3/TPR-Met |
| 52       | 54.5                                      | 50.3                                     | 24.5                                       |                   |                                                     |                                                  |              |
| 53       | 74.1                                      | 68.4                                     | 67.5                                       |                   | 90.9                                                |                                                  | BaF3/TPR-Met |
| 54       | 62.1                                      | 57.9                                     | 55.9                                       |                   | 89.6                                                | 88.3                                             | BaF3/TPR-Met |
| 55       | 60.8                                      | 58.3                                     | 58.8                                       | 1.3 $\pm$ 0.1     | 89.8                                                | 89.3                                             | BaF3/TPR-M   |

| Compound | Average inhibition rate at 10 $\mu$ M (%) | Average inhibition rate at 1 $\mu$ M (%) | Average inhibition rate at 0.1 $\mu$ M (%) | IC50 (nM)       | Cell proliferation inhibition rate at 1 $\mu$ M (%) | Cell proliferation inhibition rate at 200 nM (%) | Cell line    |
|----------|-------------------------------------------|------------------------------------------|--------------------------------------------|-----------------|-----------------------------------------------------|--------------------------------------------------|--------------|
|          |                                           |                                          |                                            |                 |                                                     |                                                  | et           |
| 56       | 58.9                                      | 56.3                                     | 53.3                                       |                 | 90.6                                                | 79.1                                             | BaF3/TPR-Met |
| 57       | 60.3                                      | 54.5                                     | 52.4                                       |                 | 89.5                                                | 86.8                                             | BaF3/TPR-Met |
| 58       | 57.4                                      | 55.7                                     | 52.8                                       |                 |                                                     |                                                  | BaF3/TPR-Met |
| 59       | 59.8                                      | 51.9                                     | 51.6                                       |                 | 89.8                                                | 70.6                                             | BaF3/TPR-Met |
| 60       | 62.6                                      | 53.4                                     | 50.1                                       |                 | 89.4                                                | 84.8                                             | BaF3/TPR-Met |
| 61       | 83.2                                      | 76                                       | 73.7                                       |                 | 91.7                                                | 83.1                                             | BaF3/TPR-Met |
| 62       | 80                                        | 73.2                                     | 73.2                                       |                 |                                                     |                                                  | BaF3/TPR-Met |
| 63       | 63                                        | 60.4                                     | 59                                         |                 | 66.5                                                |                                                  | BaF3/TPR-Met |
| 64       | 66                                        | 60.4                                     | 59.1                                       |                 | 76.4                                                |                                                  | BaF3/TPR-Met |
| 65       | 69.8                                      | 65.1                                     | 60.8                                       |                 |                                                     |                                                  | BaF3/TPR-Met |
| 66       | 79.9                                      | 75.8                                     | 73.3                                       |                 | 92.7                                                |                                                  | BaF3/TPR-Met |
| 67       | 68.2                                      | 64.6                                     | 63.1                                       |                 | 91.6                                                | 90.3                                             | BaF3/TPR-Met |
| 68       | 62                                        | 55.8                                     | 50.2                                       |                 |                                                     |                                                  | BaF3/TPR-Met |
| 69       | 59.6                                      | 57.7                                     | 52.3                                       |                 |                                                     |                                                  |              |
| 70       | 79.3                                      | 44.7                                     |                                            |                 |                                                     |                                                  |              |
| 71       | 83.8                                      | 73.4                                     | 68.5                                       | 0.1 $\pm$ 0.01  |                                                     |                                                  | MKN45        |
| 72       | 76.5                                      | 80.3                                     | 70.1                                       | 0.04 $\pm$ 0.04 | 72.8                                                |                                                  | MKN45        |
| 73       | 76.9                                      | 72.8                                     | 78                                         |                 | 14.4                                                |                                                  | MKN45        |
| 74       | 12.1                                      |                                          |                                            |                 |                                                     |                                                  |              |
| 75       | 83.1                                      | 75.6                                     | 74.6                                       |                 |                                                     |                                                  | MKN45        |
| 76       | 78.3                                      | 75.5                                     | 78                                         |                 | 14.9                                                |                                                  | MKN45        |
| 77       | 85.5                                      | 64.8                                     | 55.8                                       |                 |                                                     |                                                  | MKN45        |
| 78       | 89.3                                      | 69.3                                     | 64.5                                       |                 |                                                     |                                                  | MKN45        |
| 79       | 77.4                                      | 30.5                                     |                                            |                 |                                                     |                                                  |              |
| 80       | 80.6                                      | 47.5                                     |                                            |                 |                                                     |                                                  |              |
| 81       | 80.2                                      | 73.6                                     | 72.9                                       |                 | 24.7                                                |                                                  | MKN45        |
| 82       | 77.7                                      | 63.8                                     | 54.4                                       |                 |                                                     |                                                  | MKN45        |
| 83       | 77.7                                      | 44.4                                     |                                            |                 |                                                     |                                                  |              |
| 84       | 73.5                                      | 41.2                                     |                                            |                 |                                                     |                                                  |              |
| 85       | 79.4                                      | 30.1                                     |                                            |                 |                                                     |                                                  |              |
| 86       | 77.8                                      | 66.6                                     | 45                                         |                 |                                                     |                                                  |              |
| 87       | 72.5                                      | 72.7                                     | 33.8                                       |                 |                                                     |                                                  |              |
| 88       | 64.5                                      | 59.4                                     | 1.1                                        |                 |                                                     |                                                  |              |
| 89       | 83.4                                      | 79.9                                     | 45.3                                       |                 |                                                     |                                                  |              |
| 90       | 81.1                                      | 83                                       | 69                                         |                 | 17.6                                                |                                                  | MKN45        |
| 91       | 74.1                                      | 85.5                                     | 77.3                                       |                 | 72.9                                                |                                                  | MKN45        |
| 92       | 78.9                                      | 79.1                                     | 82.8                                       |                 |                                                     |                                                  | MKN45        |
| 93       | 77.9                                      | 76.8                                     | 76.1                                       |                 |                                                     |                                                  | MKN45        |
| 94       | 83.9                                      | 55.7                                     | 72.1                                       |                 |                                                     |                                                  | MKN45        |
| 95       | 63.4                                      | 57.1                                     | 62.7                                       |                 | 65.5                                                | 42.3                                             | MKN45        |

| Compound | Average inhibition rate at 10 $\mu$ M (%) | Average inhibition rate at 1 $\mu$ M (%) | Average inhibition rate at 0.1 $\mu$ M (%) | IC50 (nM)        | Cell proliferation inhibition rate at 1 $\mu$ M (%) | Cell proliferation inhibition rate at 200 nM (%) | Cell line |
|----------|-------------------------------------------|------------------------------------------|--------------------------------------------|------------------|-----------------------------------------------------|--------------------------------------------------|-----------|
| 96       | 68.3                                      | 61.5                                     | 56.6                                       | 0.7 $\pm$ 0.1    |                                                     |                                                  | MKN45     |
| 97       | 65.5                                      | 62.7                                     | 51.7                                       | 0.5 $\pm$ 0.1    | 67.8                                                |                                                  | MKN45     |
| 98       | 74.3                                      | 66.8                                     | 50.6                                       | 1.4 $\pm$ 0.1    |                                                     |                                                  | MKN45     |
| 99       | 71.8                                      | 66.2                                     | 55.5                                       |                  | 67.9                                                | 48.5                                             | MKN45     |
| 100      | 85.4                                      | 87.3                                     | 83.7                                       |                  | 66.6                                                | 63.8                                             | MKN45     |
| 101      |                                           | 100                                      | 100                                        | 0.3 $\pm$ 0.1    |                                                     |                                                  |           |
| 102      | 95.4                                      | 85.3                                     | 73.7                                       |                  | 67.9                                                | 63.8                                             | MKN45     |
| 103      |                                           | 100.7                                    | 98.5                                       | 3.2 $\pm$ 0.3    | 92.7                                                | 80.9                                             | EBC-1     |
| 104      |                                           | 100.5                                    | 99.8                                       | 2.1 $\pm$ 0.6    | 89.2                                                | 85.7                                             | EBC-1     |
| 105      |                                           | 100.3                                    | 97.8                                       | 2.6 $\pm$ 0.4    | 91.5                                                | 77.7                                             | EBC-1     |
| 106      |                                           | 100.6                                    | 103.9                                      | 1.9 $\pm$ 0.1    | 85.7                                                | 37.0                                             | EBC-1     |
| 107      |                                           | 88.2                                     | 29.1                                       |                  | 18.1                                                | 18.9                                             | EBC-1     |
| 108      |                                           | 61.4                                     | 9.1                                        |                  | 20.6                                                | 15.4                                             | EBC-1     |
| 109      |                                           | 40                                       |                                            |                  |                                                     |                                                  |           |
| 110      |                                           | 13.5                                     |                                            |                  |                                                     |                                                  |           |
| 111      |                                           | 63.3                                     | 28.6                                       |                  |                                                     |                                                  |           |
| 112      |                                           | 48.8                                     |                                            |                  |                                                     |                                                  |           |
| 113      |                                           | 97.7                                     | 48.6                                       |                  | 9                                                   | 7.9                                              | EBC-1     |
| 114      |                                           | 30.4                                     |                                            |                  |                                                     |                                                  |           |
| 115      |                                           | 95.7                                     | 46.6                                       |                  |                                                     |                                                  | EBC-1     |
| 116      |                                           | 84.6                                     | 70.8                                       | 3.6 $\pm$ 0.6    |                                                     |                                                  | EBC-1     |
| 117      |                                           | 15.8                                     |                                            |                  |                                                     |                                                  |           |
| 118      |                                           | 75.5                                     | 62.7                                       |                  |                                                     |                                                  | EBC-1     |
| 119      |                                           | 26.4                                     |                                            |                  |                                                     |                                                  |           |
| 120      |                                           | 28.7                                     |                                            |                  |                                                     |                                                  |           |
| 121      |                                           | 101.1                                    | 99                                         | 9.0 $\pm$ 1.0    | 92.5                                                | 91.6                                             | EBC-1     |
| 122      |                                           | 100.5                                    | 72.9                                       | 189.7 $\pm$ 32.7 |                                                     |                                                  | EBC-1     |
| 123      |                                           | 99.3                                     | 87                                         | 51.5 $\pm$ 6.0   |                                                     |                                                  | EBC-1     |
| 124      |                                           | 99.7                                     | 94.4                                       | 4.7 $\pm$ 1.0    | 92.7                                                | 43.1                                             | EBC-1     |
| 125      |                                           | 99.3                                     | 84.5                                       | 55.2 $\pm$ 5.6   |                                                     |                                                  | EBC-1     |
| 126      |                                           | 100.1                                    | 100                                        | 7.3 $\pm$ 1.1    | 87                                                  | 35.1                                             | EBC-1     |
| 127      |                                           | 99                                       | 93.9                                       | 30.0 $\pm$ 3.3   |                                                     |                                                  | EBC-1     |
| 128      |                                           | 99.3                                     | 99.4                                       | 2.0 $\pm$ 0.2    | 87                                                  | 80.6                                             | EBC-1     |
| 129      |                                           | 101.2                                    | 99.6                                       | 2.7 $\pm$ 0.5    | 86.6                                                | 79                                               | EBC-1     |
| 130      |                                           | 90.8                                     | 16.1                                       |                  |                                                     |                                                  | EBC-1     |
| 131      |                                           | 83.6                                     | 75.1                                       |                  |                                                     |                                                  | EBC-1     |
| 132      |                                           | 100                                      | 92.1                                       |                  | 85.4                                                | 48.2                                             | EBC-1     |
| 133      |                                           | 100                                      | 100                                        | 2.6 $\pm$ 0.2    | 87.8                                                | 86.4                                             | EBC-1     |
| 134      |                                           | 56.9                                     | 66.8                                       |                  |                                                     |                                                  | EBC-1     |
| 135      |                                           | 88.2                                     | 87.4                                       | 2.6 $\pm$ 0.2    | 91.4                                                | 89.4                                             | EBC-1     |
| 136      |                                           | 91.3                                     | 90.2                                       | 1.2 $\pm$ 0.1    | 92.4                                                | 91.4                                             | EBC-1     |
| 137      |                                           | 89.9                                     | 91.6                                       | 1.3 $\pm$ 0.1    | 92.4                                                | 73                                               | EBC-1     |
| 138      |                                           | 90.5                                     | 87.7                                       | 0.6 $\pm$ 0.01   | 92.9                                                | 90.9                                             | EBC-1     |
| 139      |                                           | 88.9                                     | 90.3                                       | 1.0 $\pm$ 0.1    | 91.6                                                | 90.7                                             | EBC-1     |
| 140      |                                           | 89.5                                     | 92.4                                       | 0.5 $\pm$ 0.03   | 92                                                  | 91.4                                             | EBC-1     |
| 141      |                                           | 88.5                                     | 86.3                                       | 0.3 $\pm$ 0.1    | 92.7                                                | 92.6                                             | EBC-1     |
| 142      |                                           | 91.3                                     | 89.4                                       | 0.5 $\pm$ 0.1    | 92.6                                                | 92.1                                             | EBC-1     |
| 143      |                                           | 92.1                                     | 90                                         | 0.4 $\pm$ 0.1    | 92.5                                                | 92.3                                             | EBC-1     |
| 144      |                                           | 93.1                                     | 92.1                                       | 0.3 $\pm$ 0.01   | 91.4                                                | 91.1                                             | EBC-1     |
| 145      |                                           | 87.1                                     | 90.6                                       | 0.6 $\pm$ 0.1    | 92.8                                                | 92.4                                             | EBC-1     |

#### Test IV: Effect of compounds on human non-small cell lung cancer cell EBC-1

## **xenograft growth in nude mice**

### **1. Test method**

EBC-1 cells were implanted subcutaneously in the right axilla of nude mice at  $5 \times 10^6$  cells per mouse, xenograft developed thereby was passaged in nude mice for 3 generations prior to use. Tumor tissue at rapid growth phase was taken, minced under sterile condition into pieces of about  $1.5 \text{ mm}^3$ , then implanted subcutaneously in the right axilla of nude mice. Xenografted tumor diameters were determined by caliper measurements, when the tumor grew to give a tumor volume of  $100\text{--}200 \text{ mm}^3$ , the animals were randomized into groups based on the tumor volume, 12 animals in the vehicle control group, and 6 animals in each test group. The test groups were administered orally with compound 142 or 145 (50mg/kg, 100mg/kg), the administration was made daily for 21 consecutive days, while the vehicle control group was administered with equivalent amount of solvent (0.5% sodium carboxymethyl cellulose).

Xenografted tumor diameters were measured twice per week, and body weights of the mice were measured at the same time. Tumor Volume (TV) was calculated by the following equation:  $TV = 1/2 \times a \times b^2$ , wherein a, b refers to the length and width, respectively. Based on the measurement, Relative Tumor Volume (RTV) was calculated by the following equation:  $RTV = V_t/V_0$ , wherein  $V_0$  is the tumor volume measured when divided for administration (i.e.,  $d_0$ ),  $V_t$  is the tumor volume measured at each timepoint.

Antitumor activity is evaluated by the following indices: 1) relative tumor proliferation rate T/C(%), calculated by the following equation:  $T/C(\%) = (T_{RTV}/C_{RTV}) \times 100\%$ ,  $T_{RTV}$ : RTV of treatment group;  $C_{RTV}$ : RTV of negative control group; 2) inhibition rate of tumor volume increase GI%, calculated by the following equation:  $GI\% = [1 - (TV_t - TV_0)/(CV_t - CV_0)] \times 100\%$ ,  $TV_t$  is the tumor volume of the treatment group measured at each timepoint;  $TV_0$  is the tumor volume of the treatment group measured when divided for administration;  $CV_t$  is the tumor volume of the control group measured at each timepoint;  $CV_0$  is the tumor volume of the control group measured when divided for administration.

### **2. Test result**

When administration was completed (d21), compound 142 exhibited very significant

dose dependent inhibition against the tumor growth of human lung cancer EBC-1 subcutaneous xenograft in nude mice, 100mg/kg and 50mg/kg dosage groups obtained T/C percentages of 1.05% and 16.91%, respectively, at day 21, in 100mg/kg dosage group, two mice exhibited complete tumor regression at day 11 and four mice exhibited complete tumor regression by the end of the trial. Compound 145 exhibited very significant dose dependent inhibition against the tumor growth of human lung cancer EBC-1 subcutaneous xenograft in nude mice, 100mg/kg and 50mg/kg dosage groups obtained T/C percentages of 0.40% and 2.36%, respectively, at day 21; in 100mg/kg dosage group, two mice exhibited complete tumor regression at day 11 and four mice exhibited complete tumor regression by the end of the trial; in 50mg/kg dosage group, two mice exhibited complete tumor regression at day 18 and three mice exhibited complete tumor regression by the end of the trial. During the administration period, mice in all treatment groups were in good state and were survived (Fig. 1).

**Table 3 Experimental therapeutic effect of compounds on human lung cancer**

**EBC-1 xenograft in nude mice**

| Group           | Dosage, mode of administration |    |    | Animal number  |                 | Weight (g)     |                 | TV (mm <sup>3</sup> , mean±SD) |                 | RTV (mean±SD) | T/C (%) | GI (%) |
|-----------------|--------------------------------|----|----|----------------|-----------------|----------------|-----------------|--------------------------------|-----------------|---------------|---------|--------|
|                 |                                |    |    | d <sub>0</sub> | d <sub>21</sub> | d <sub>0</sub> | d <sub>21</sub> | d <sub>0</sub>                 | d <sub>21</sub> |               |         |        |
| Vehicle control | 0.2ml/anima                    | po | 12 | 12             | 17.9            | 22.8           | 126±31          | 1606±362                       | 13.18±3.39      |               |         |        |
| 142             | 100mg/kg qd/21                 | po | 6  | 6              | 17.8            | 20.9           | 120±30          | 21±34(4)                       | 0.14±0.21***    | 1.05          | 106.70  |        |
|                 | 50mg/kg qd/21                  | po | 6  | 6              | 17.7            | 21.0           | 120±25          | 259±421                        | 2.23±3.89***    | 16.91         | 90.65   |        |
| 145             | 100mg/kg qd/21                 | po | 6  | 6              | 16.9            | 19.1           | 123±27          | 8±13(4)                        | 0.05±0.09***    | 0.40          | 107.77  |        |
|                 | 50mg/kg qd/21                  | po | 6  | 6              | 16.8            | 19.9           | 127±32          | 36±49(3)                       | 0.31±0.50***    | 2.36          | 106.14  |        |

t student's test vs vehicle control, \*\*\*, p<0.001 numbers in parenthesis are the numbers of mice exhibiting complete tumor regression

**Test V: Effect of compound on human malignant glioblastoma cell U87MG xenograft in nude mice**

**1. Test method**

U87-MG cells were expanded by *in vitro* culture, cells at log phase were harvested and resuspended in EMEM, adjusted to a cell density of 2.8×10<sup>7</sup>/mL, then implanted subcutaneously in the right axilla of nude mice. Animals and the growth status of the

xenograft were monitored periodically, when tumor volume generally reached 100~300 mm<sup>3</sup>, animals bearing tumor in too big size, too small size, or in irregular shape were eliminated, and the remaining tumor bearing mice were randomized into 2 groups based on the tumor volume, one vehicle control group (5%DMAC containing 0.5% methylcellulose), and one test group receiving Sample 19 at 50mg/kg daily for 14 consecutive days.

During the trial, tumor diameters and animal weights were measured twice a week. Tumor Volume (TV) was calculated by the following equation:  $TV = 1/2 \times a \times b^2$ , wherein a, b represent length and width, respectively. Based on the measurement, Relative Tumor Volume (RTV) was calculated by the following equation:  $RTV = V_t/V_0$ , wherein  $V_0$  is the tumor volume measured when divided for administration (i.e.,  $d_0$ ),  $V_t$  is the tumor volume measured at each timepoint. Antitumor activity is evaluated by the following indices: 1) relative tumor proliferation rate T/C(%), calculated by the following equation:  $T/C(\%) = (T_{RTV}/C_{RTV}) \times 100\%$ ,  $T_{RTV}$ : RTV of treatment group;  $C_{RTV}$ : RTV of negative control group; 2) inhibition rate of tumor volume increase GI%, calculated by the following equation:  $GI\% = [1 - (TV_t - TV_0)/(CV_t - CV_0)] \times 100\%$ ,  $TV_t$  is the tumor volume of the treatment group measured at each timepoint;  $TV_0$  is the tumor volume of the treatment group measured when divided for administration;  $CV_t$  is the tumor volume of the control group measured at each timepoint;  $CV_0$  is the tumor volume of the control group measured when divided for administration.

## 2. Test result

When administration was completed (d14), test group receiving compound 19 at 50mg/kg exhibited favorable antitumor activity, relative tumor proliferation rate (%T/C) at the end of the trial was 7.29% ( $P < 0.01$ ), the test group exhibited a very significant difference in relative tumor volume when compared to the vehicle control group. During the administration period, all mice in treatment group were in good state and were survived (Fig. 2).

**Table 4. Experimental therapeutic effect of compound on U87MG xenograft in nude mice**

| Group                  | Dosage, mode of administration |    | Animal number  |                 | Weight (g)     |                 | TV (mm <sup>3</sup> , mean±SE) |                 | RTV (mean ±SE) | T/C (%) | GI (%) |
|------------------------|--------------------------------|----|----------------|-----------------|----------------|-----------------|--------------------------------|-----------------|----------------|---------|--------|
|                        |                                |    | d <sub>0</sub> | d <sub>14</sub> | d <sub>0</sub> | d <sub>21</sub> | d <sub>0</sub>                 | d <sub>21</sub> |                |         |        |
| <b>Vehicle control</b> | 0.25ml/animal qd/14            | po | 12             | 12              | 23.5           | 24.6            | 182 ±22                        | 1846 ±149       | 1056.3 ±92.2   |         |        |
| <b>19</b>              | 50mg/kg qd/14                  | po | 6              | 6               | 24.2           | 24.5            | 180 ±20                        | 140 ±20         | 77.0 ±5.2**    | 7.29    | 102.41 |

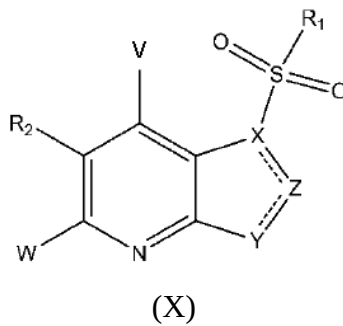
t student's test vs vehicle control group, \*\*, p<0.01

Although the present invention is described referring to specific examples, it is obvious to a person skilled in the art that numerous modifications and variations may be made to this invention without departing from the spirit and scope of the present invention. Accordingly, the appended claims cover all these modifications within the scope of this invention. All publications, patents and patent applications cited herein are incorporated herein by reference.

## CLAIMS

What is claimed is:

1. A 5-member-heterocycle-fused pyridine compound having a structure of Formula (X), pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof,



wherein X, Y and Z are each independently N or C, at least one of X, Y and Z is N, and Y and Z are unsubstituted; provided that when X is N, Z is N;

— — — represents a single bond or double bond, and X, Y and Z abide by valence-bond theory;

W and V are each independently selected from the group consisting of H, halogen, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkoxy, nitro, and cyano;

R<sub>1</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, hydroxyl; unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), -OC(O)-R<sub>f</sub>, unsubstituted phenyl or phenyl substituted by 1-4 of R<sub>3</sub>, or unsubstituted 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S, or 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S substituted by 1-4 of R<sub>4</sub>;

R<sub>2</sub> is cyano; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl; -NR<sub>c</sub>R<sub>d</sub>; substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S;

wherein, substituent in the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or -NR<sub>c</sub>R<sub>d</sub>-substituted C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, morpholinylmethyl, or unsubstituted or R''-substituted piperidinyl;

wherein R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl-substituted piperidinyl;

R' is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heterocyclyl;

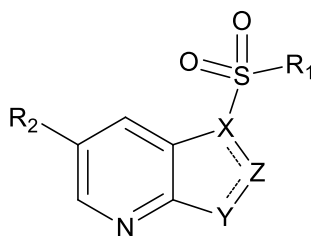
R'' is C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from the group consisting of halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>a</sub> and R<sub>b</sub> are each independently H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl;

R<sub>c</sub> and R<sub>d</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; or, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl;

R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heteroaryl.

2. The 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, according to claim 1, wherein, the compound has a structure of Formula (I),



I

wherein,

X, Y and Z are each independently N or C, at least one of X, Y and Z is N, and Y and Z are unsubstituted; provided that when X is N, Z is N;

$\text{---}$  represents a single bond or double bond, and X, Y and Z abide by valence-bond theory;

R<sub>1</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), unsubstituted phenyl or phenyl substituted by 1-4 of R<sub>3</sub>, or unsubstituted 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S, or 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S substituted by 1-4 of R<sub>4</sub>;

R<sub>2</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected the group consisting of from N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or -NR<sub>c</sub>R<sub>d</sub>-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl;

wherein, R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl-substituted piperidinyl;

R' is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heterocyclyl;

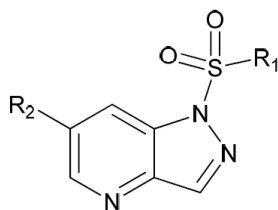
R'' is C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from the group consisting of halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>a</sub> and R<sub>b</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>c</sub> and R<sub>d</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; or, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl.

3. The 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, according to claim 1, wherein X and Z are N, Y is CH.

4. The 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, according to claim 3, wherein the 5-member-heterocycle-fused pyridine compound has a structure of Formula (II),



(II)

wherein:

R<sub>1</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, hydroxyl, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), unsubstituted phenyl or phenyl substituted by 1-4 of R<sub>3</sub>, or unsubstituted 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S, or 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S substituted by 1-4 of R<sub>4</sub>;

R<sub>2</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or -NR<sub>c</sub>R<sub>d</sub>-substituted C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl;

R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkoxy-carbonyl-substituted piperidinyl;

R' is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heterocyclyl;

R'' is C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>6</sub> alkoxy-carbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from the group consisting of halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>a</sub> and R<sub>b</sub> are each independently H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl; and

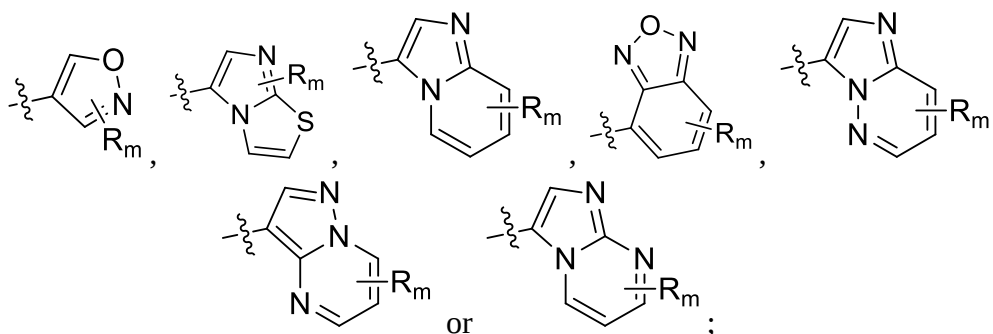
R<sub>c</sub> and R<sub>d</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; or, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl.

5. The 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, according to claim 1,

wherein, W and V are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

X and Z are N, Y is CH;

R<sub>1</sub> is



wherein, R<sub>m</sub> is H, halogen, nitro, cyano; unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>4</sub> alkoxy-carbonyl; -NR<sub>a</sub>R<sub>b</sub>; -C(O)(NR<sub>a</sub>R<sub>b</sub>); -OC(O)-R<sub>f</sub>; unsubstituted phenyl or phenyl substituted by 1-3 of R<sub>3</sub>; or unsubstituted 5- to 7-membered heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, O, and S or 5- to 7-membered heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, O, and S substituted by 1-3 of R<sub>4</sub>, wherein said heteroaryl is

selected from the group consisting of furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranyl, pyridinyl, morpholinyl, oxazinyl, and pyrazinyl;

R<sub>2</sub> is cyano; C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl; -NR<sub>c</sub>R<sub>d</sub>; substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or -NR<sub>c</sub>R<sub>d</sub>-substituted C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl;

R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>2</sub> alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or 4-morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', 4-piperidinyl, or 1-t-butoxycarbonyl-4-piperidinyl;

R' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or 4-methylpiperazinyl;

R'' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkyl carbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl carbonyl, or p-trifluoromethylbenzoyl;

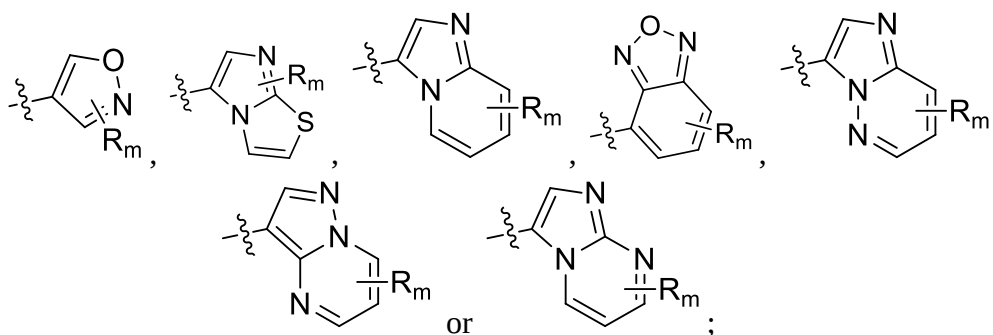
R<sub>a</sub> and R<sub>b</sub> are each independently H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkyl carbonyl;

R<sub>c</sub> and R<sub>d</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; or, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl;

R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heteroaryl, said 4- to 7-membered heteroaryl is selected from the group consisting of furanyl, pyrrolyl, and thienyl.

6. The 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, according to claim 4,

wherein R<sub>1</sub> is



wherein,  $R_m$  is H, halogen, nitro, cyano; unsubstituted or halogen- or morpholinyl-substituted  $C_1$ - $C_4$  alkyl;  $C_1$ - $C_4$  alkoxy;  $C_1$ - $C_4$  alkylcarbonyl;  $C_1$ - $C_4$  alkoxycarbonyl;  $-NR_aR_b$ ;  $-C(O)(NR_aR_b)$ ; unsubstituted phenyl or phenyl substituted by 1-3 of  $R_3$ ; or unsubstituted 5- to 7-membered heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, O, and S or 5- to 7-membered heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, O, and S substituted by 1-3 of  $R_4$ , wherein said heteroaryl is selected from the group consisting of furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranal, pyridinyl, morpholinyl, oxazinyl, and pyrazinyl;

$R_2$  is substituted or unsubstituted  $C_6$ - $C_{20}$  aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano,  $C_1$ - $C_4$  alkylendioxy, unsubstituted or halogen- or  $-NR_cR_d$ -substituted  $C_1$ - $C_6$  alkyl or  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  sulfamido,  $-NR_aR_b$ ,  $-C(O)R'$ , morpholinyl, or unsubstituted or  $R''$ -substituted piperidinyl;

$R_3$  is halogen, nitro, cyano,  $C_1$ - $C_2$  alkylendioxy, unsubstituted or halogen- or morpholinyl-substituted  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $-NR_aR_b$ ,  $-C(O)R'$ , or 4-morpholinyl;

$R_4$  is halogen, nitro, cyano, unsubstituted or halogen-substituted  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $-NR_aR_b$ ,  $-C(O)R'$ , 4-piperidinyl, or 1-t-butoxycarbonyl-4-piperidinyl;

$R'$  is  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $-NR_aR_b$ , or 4-methylpiperazinyl;

$R''$  is  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_4$  alkylcarbonyl,  $C_1$ - $C_4$  alkoxycarbonyl,  $C_3$ - $C_6$  cycloalkylcarbonyl, or p-trifluoromethylbenzoyl;

$R_a$  and  $R_b$  are each independently H,  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkylcarbonyl; and

$R_c$  and  $R_d$  are each independently H or  $C_1$ - $C_6$  alkyl; or,  $R_c$  and  $R_d$ , together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl.

7. The 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, according to claim 4,

wherein,  $R_1$  is



containing 1-3 heteroatoms selected from the group consisting of N, O, and S substituted by 1-3 of R<sub>4</sub>, wherein said heteroaryl is selected from the group consisting of furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranyl, pyridinyl, morpholinyl, oxazinyl, and pyrazinyl;

R<sub>n</sub> is H, halogen; nitro; cyano; unsubstituted or halogen-, dimethylamino-, 4-morpholinyl-, 1-aziridinyl-, 1-azetidiny-, 1-tetrahydropyrrolyl-, 1-piperidinyl- or 1-homopiperidinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> sulfamido; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; 4-morpholinyl; or unsubstituted or R''-substituted piperidinyl;

R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylendioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl;

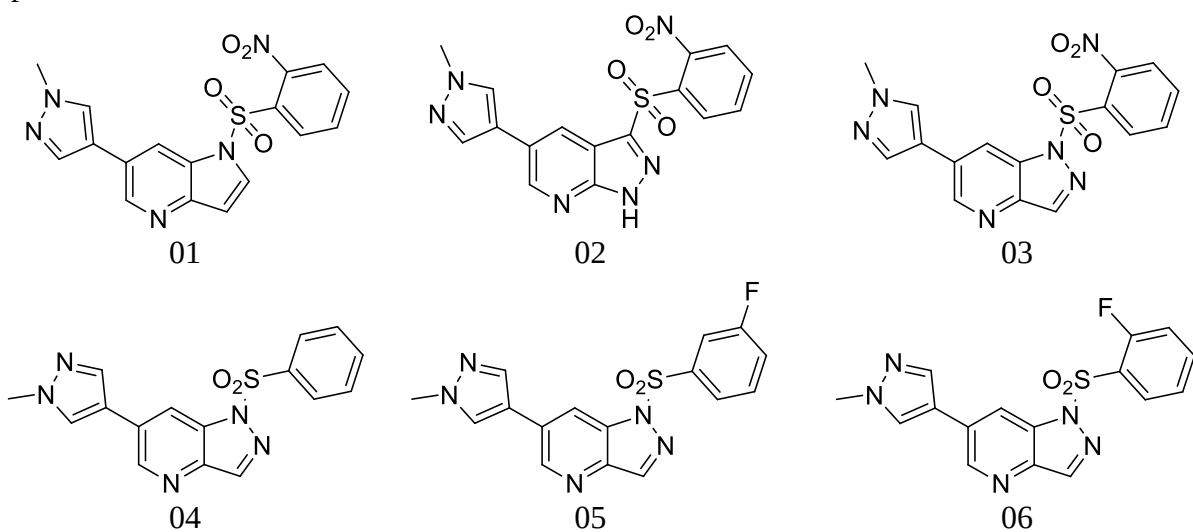
R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl-substituted piperidinyl;

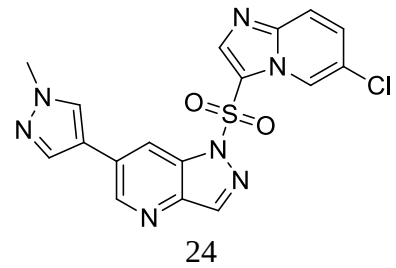
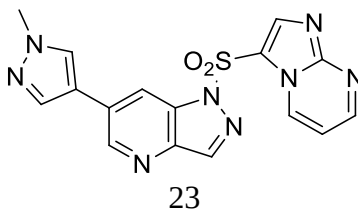
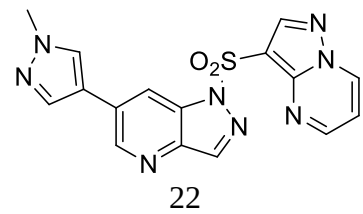
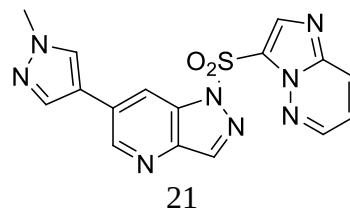
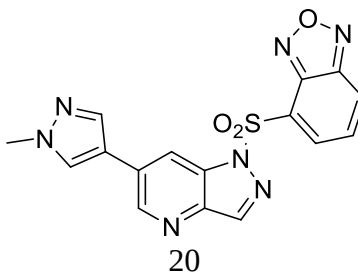
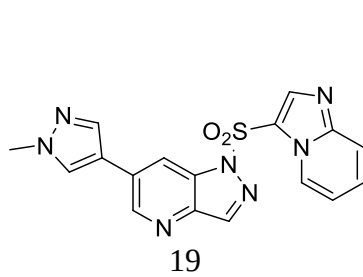
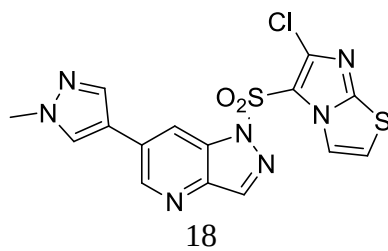
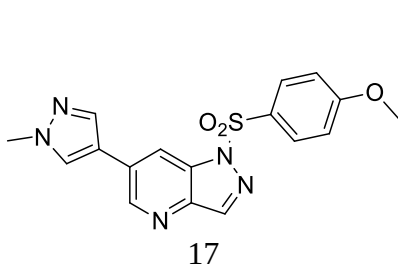
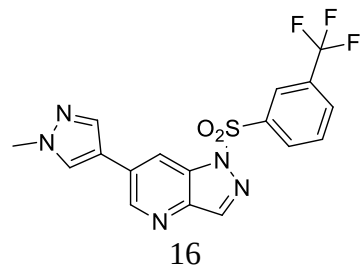
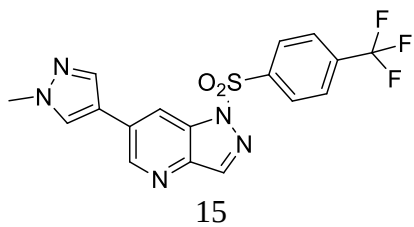
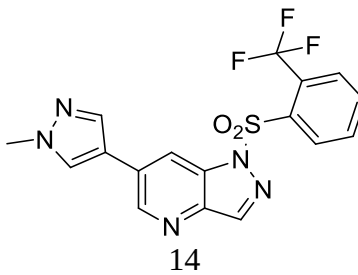
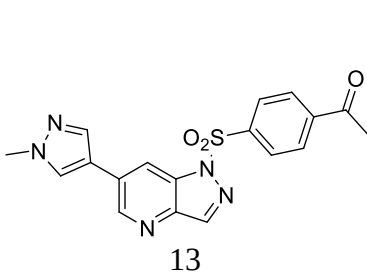
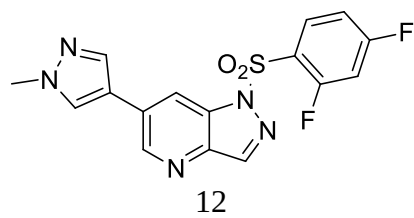
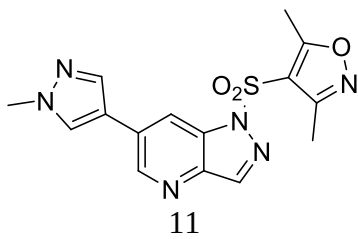
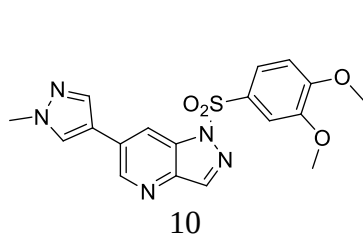
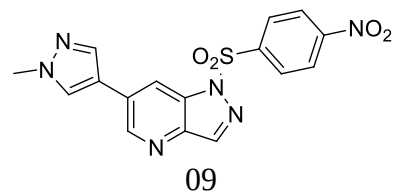
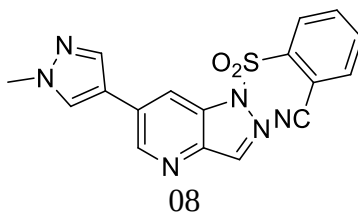
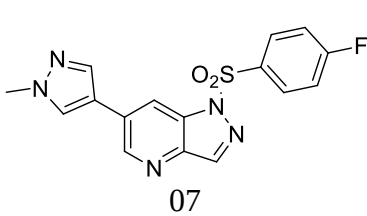
R' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or 4-methylpiperazinyl;

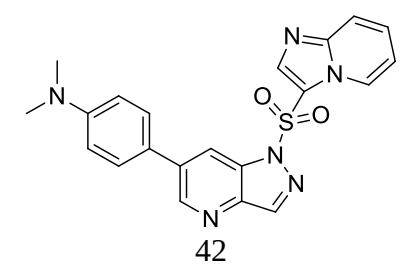
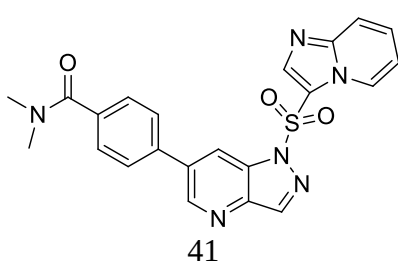
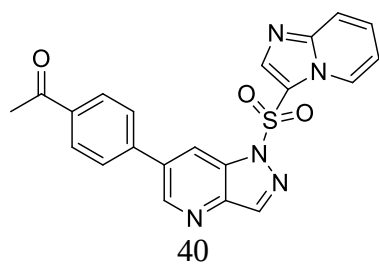
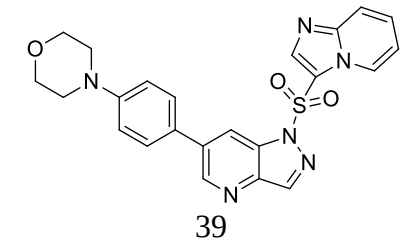
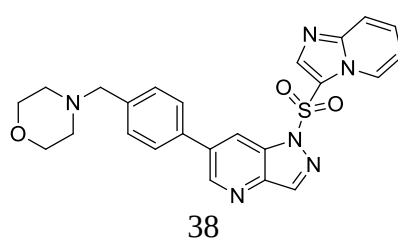
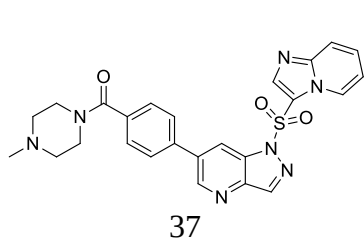
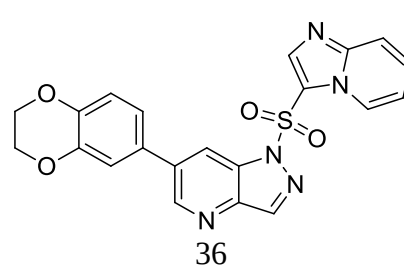
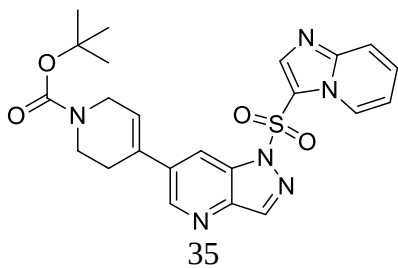
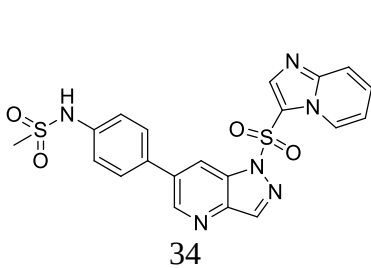
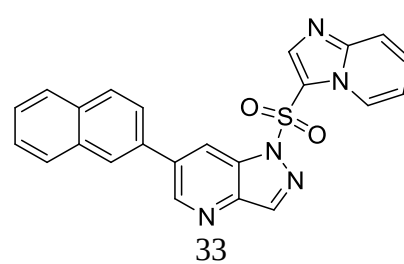
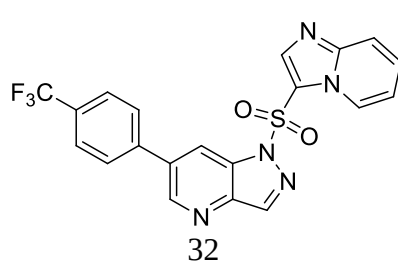
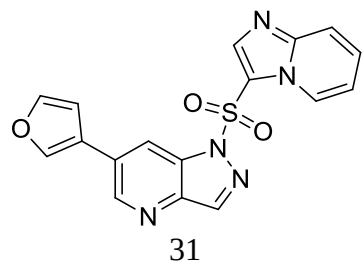
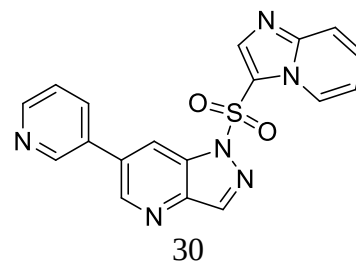
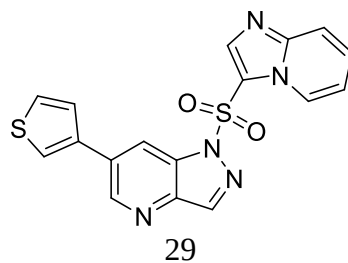
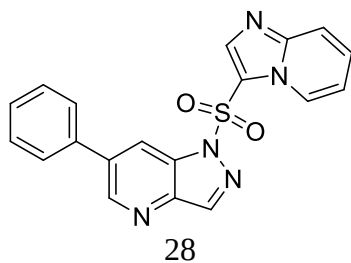
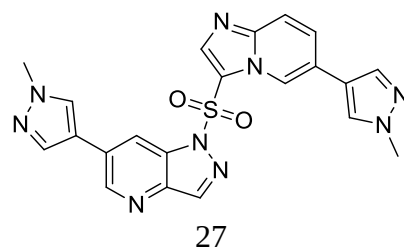
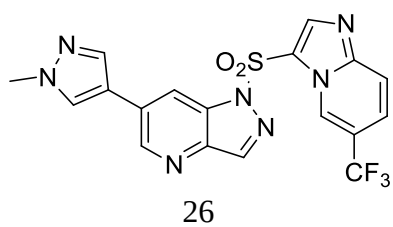
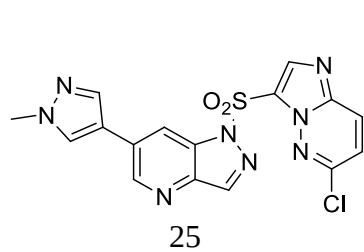
R'' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl, or p-trifluoromethylbenzoyl; and

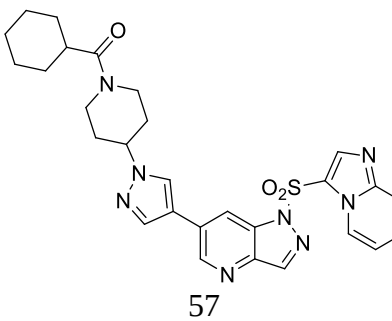
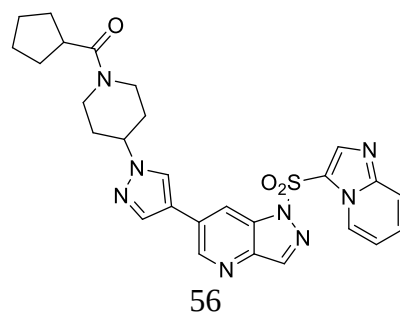
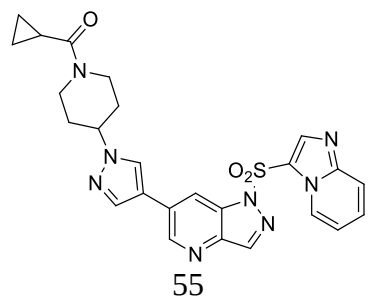
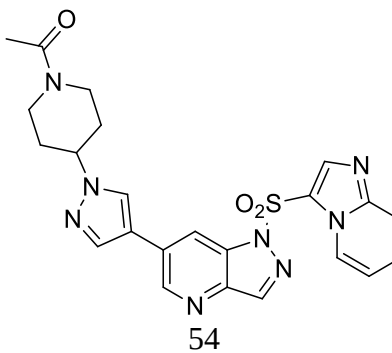
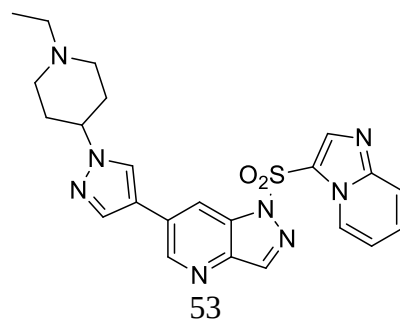
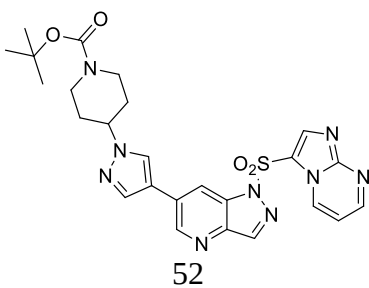
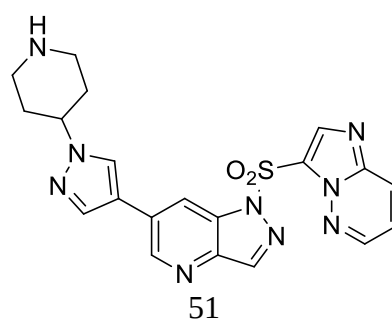
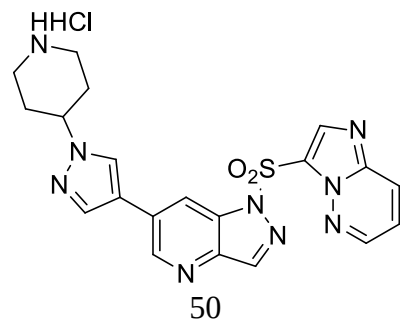
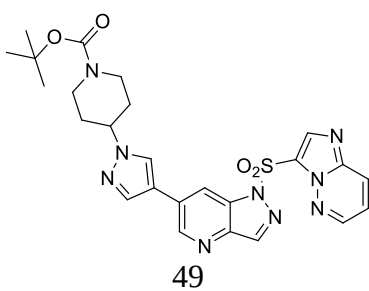
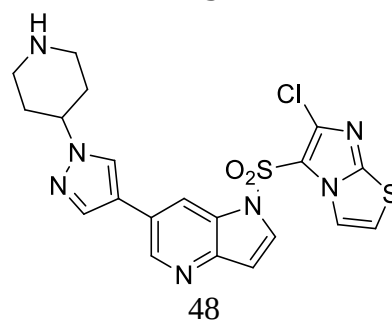
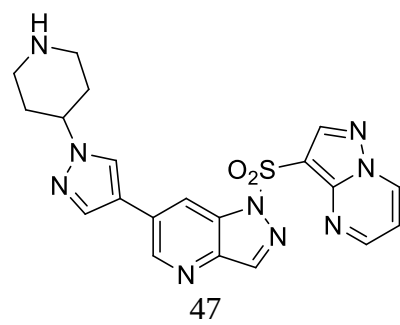
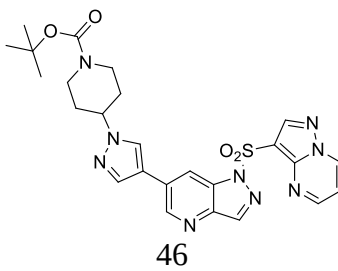
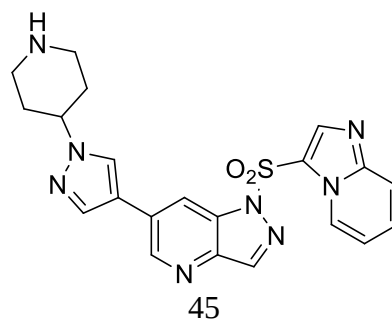
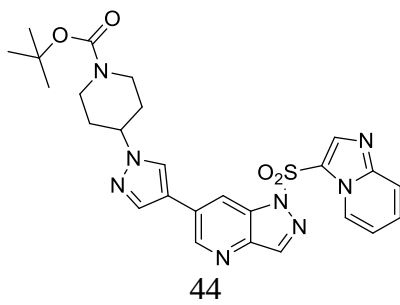
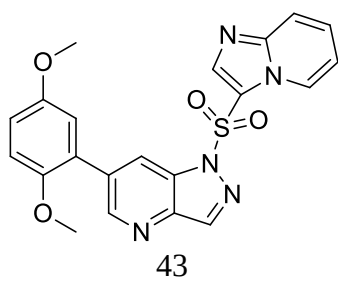
R<sub>a</sub> and R<sub>b</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl.

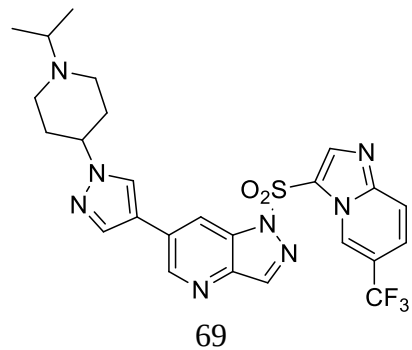
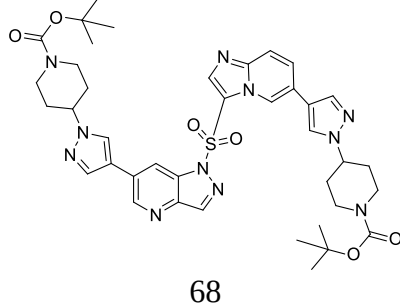
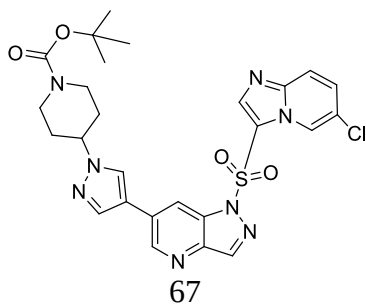
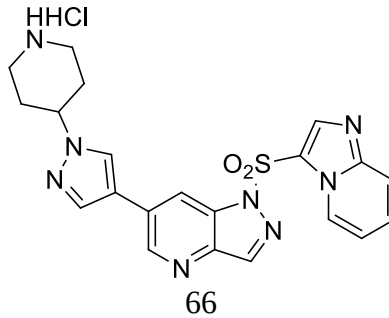
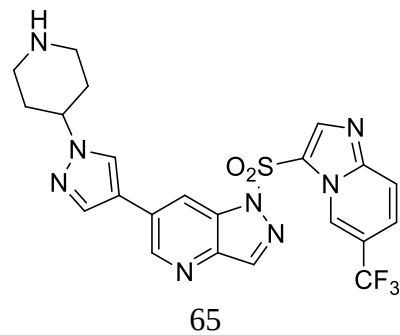
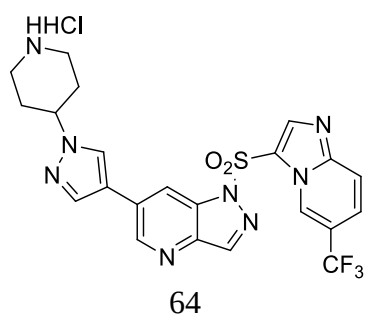
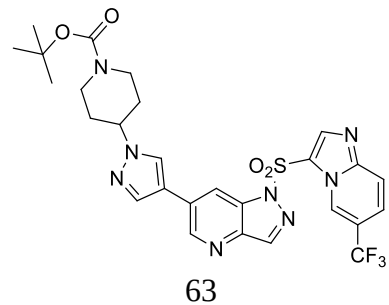
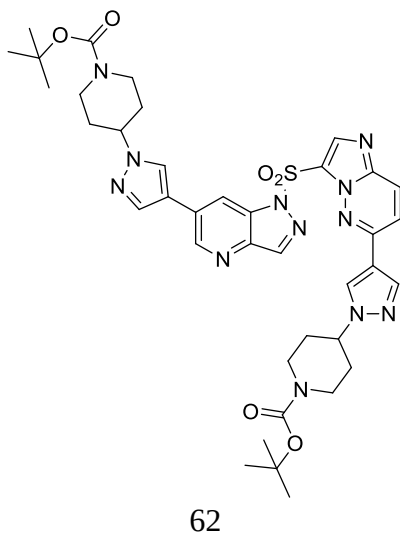
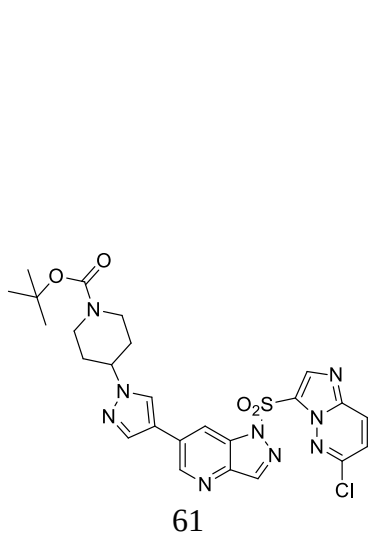
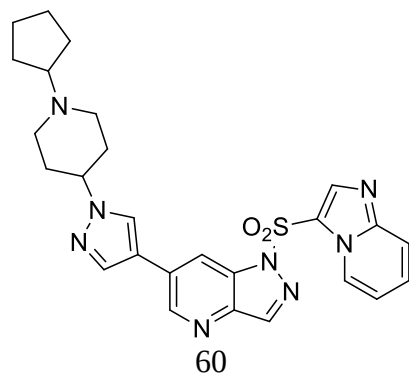
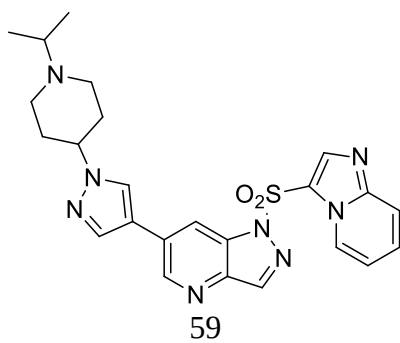
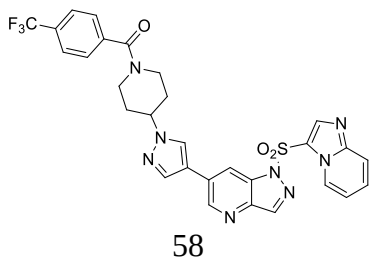
9. The 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof, according to claim 1, wherein, the 5-member-heterocycle fused pyridine compound is selected from the group consisting of the following compounds:

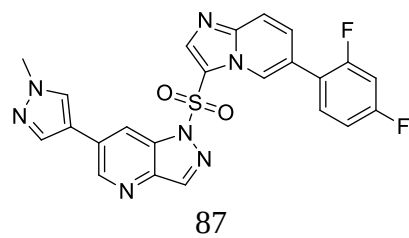
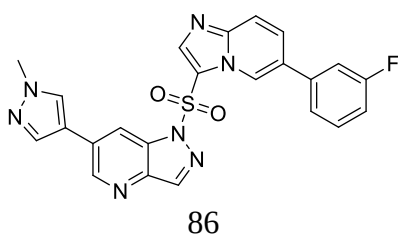
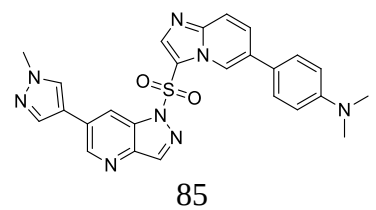
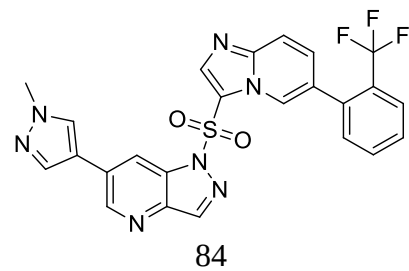
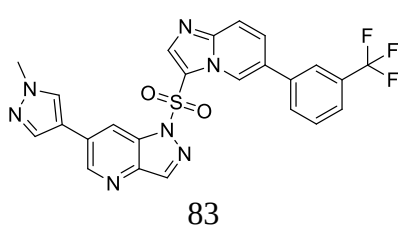
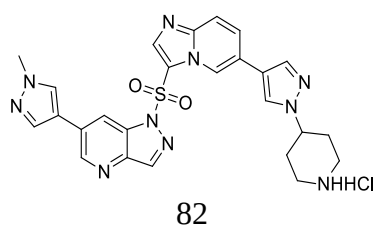
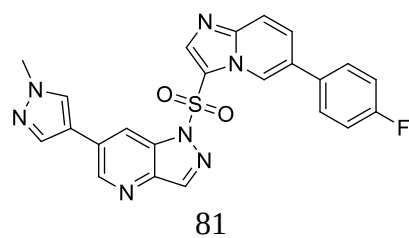
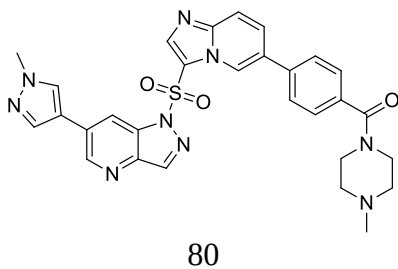
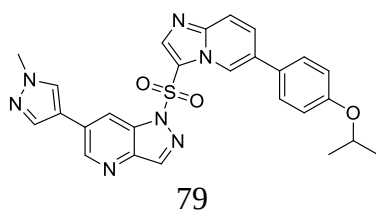
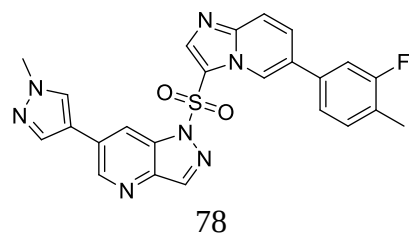
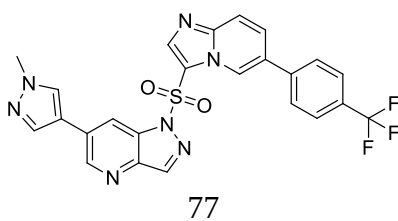
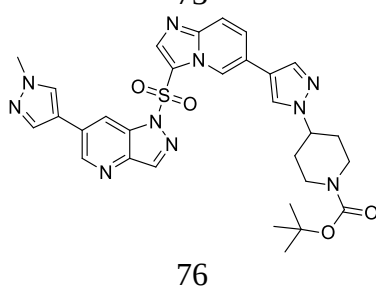
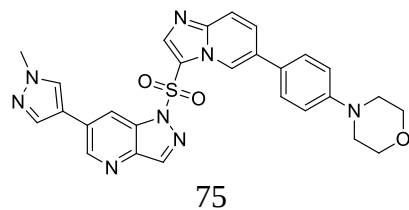
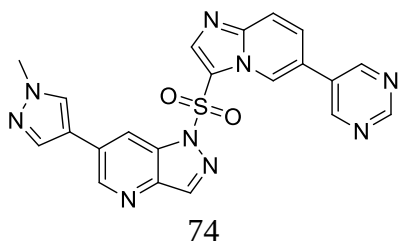
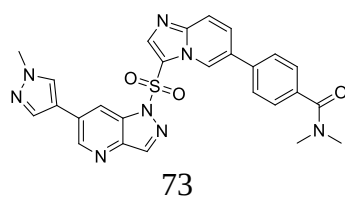
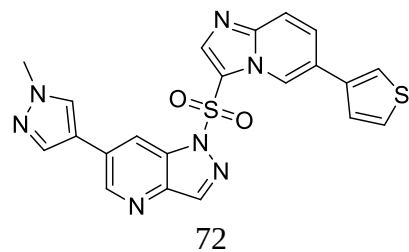
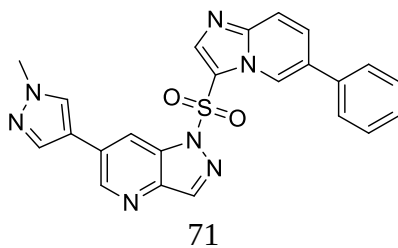
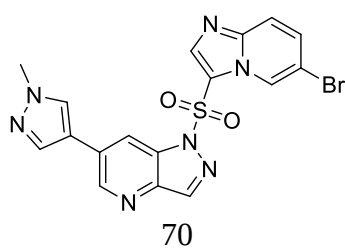


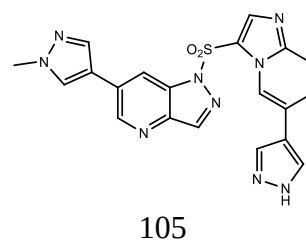
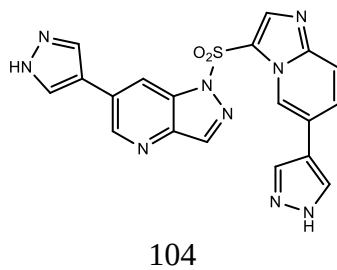
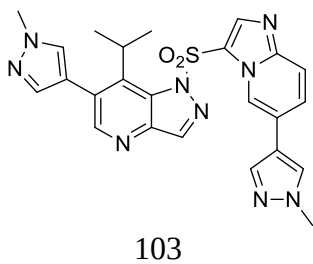
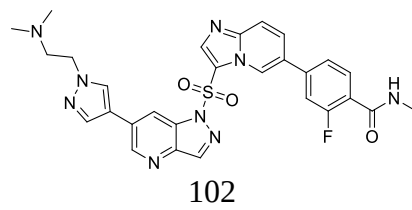
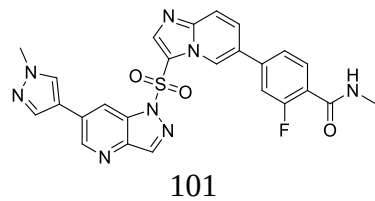
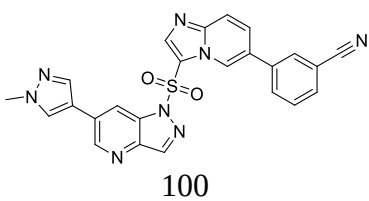
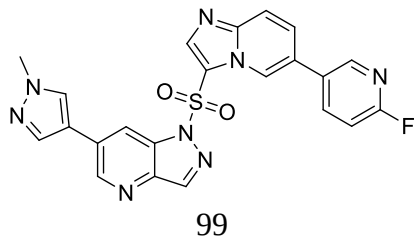
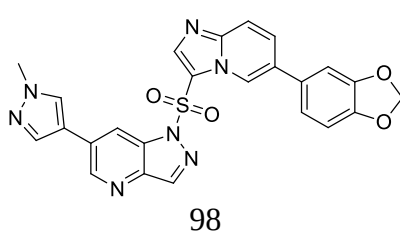
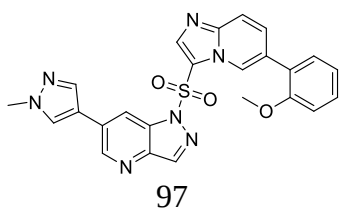
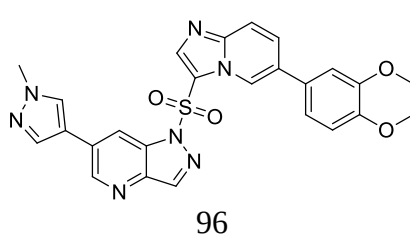
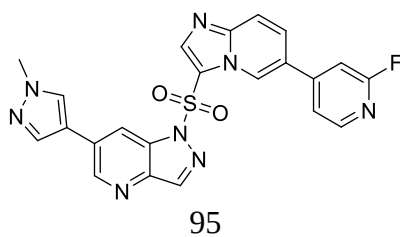
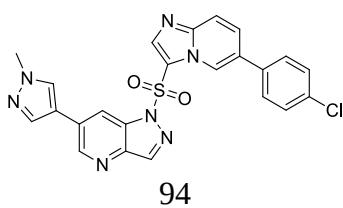
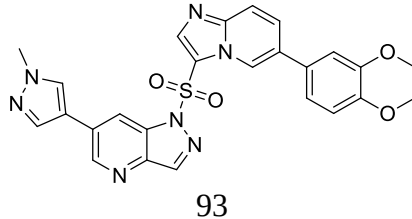
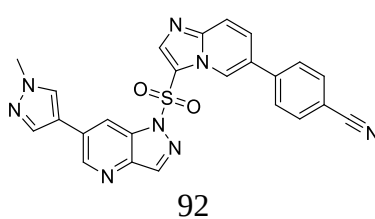
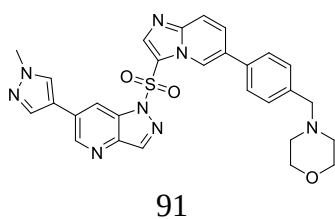
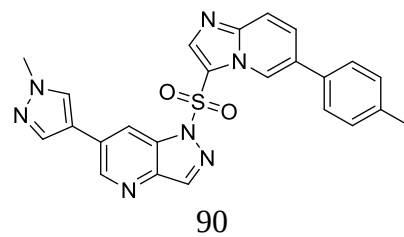
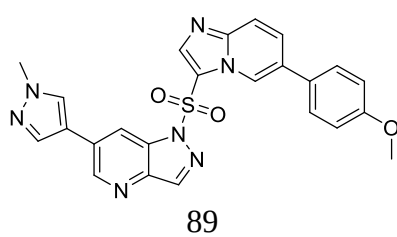
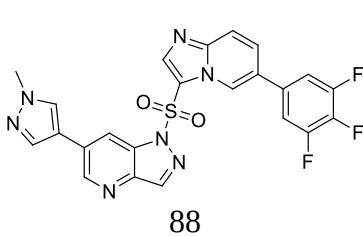


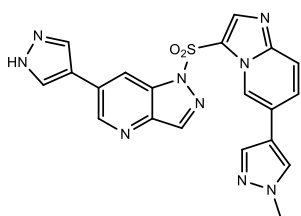




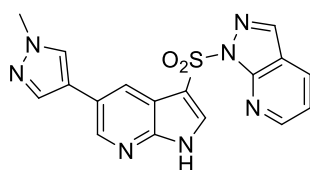




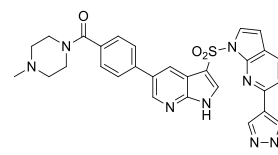




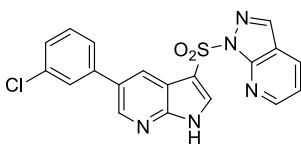
106



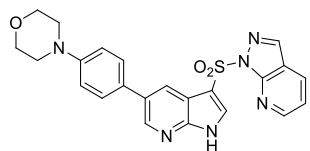
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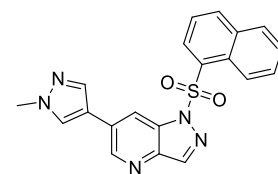
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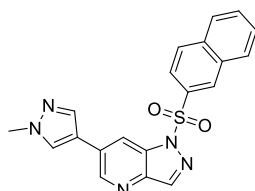
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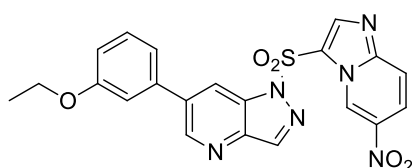
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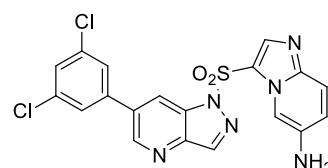
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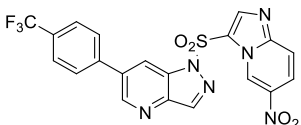
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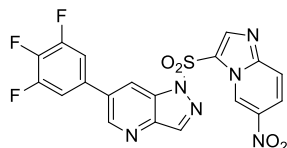
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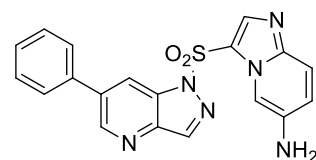
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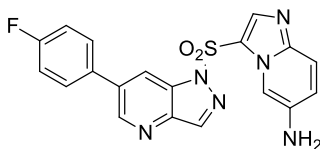
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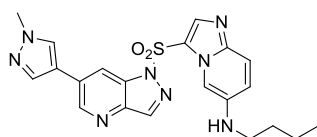
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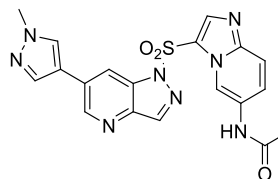
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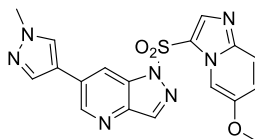
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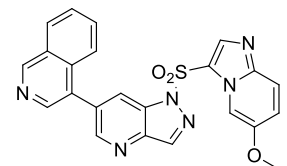
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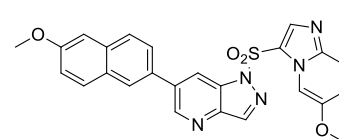
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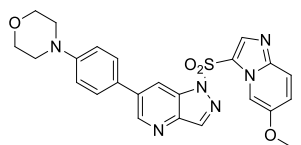
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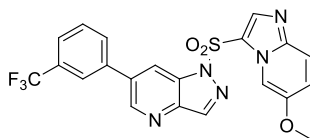
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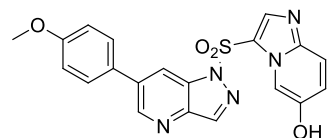
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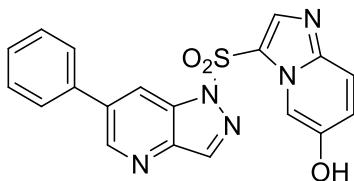
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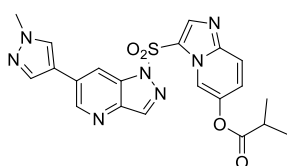
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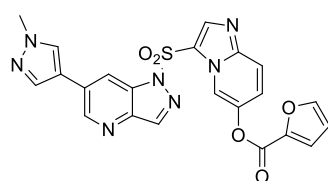
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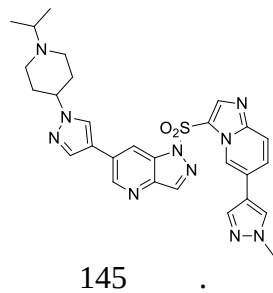
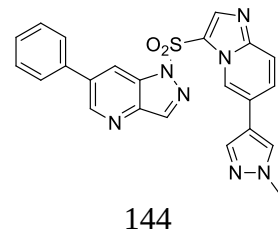
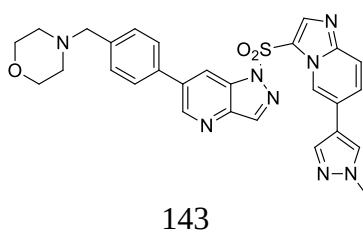
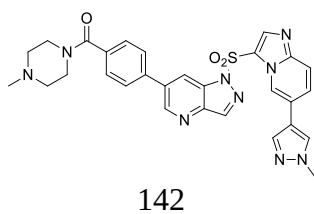
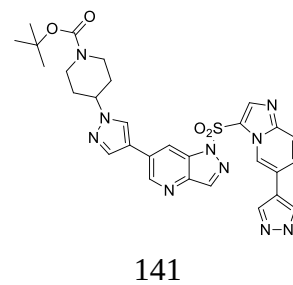
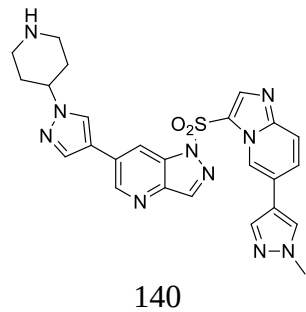
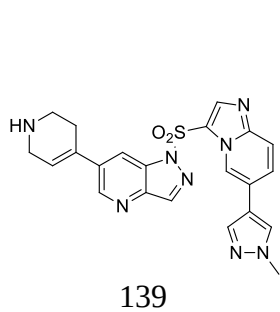
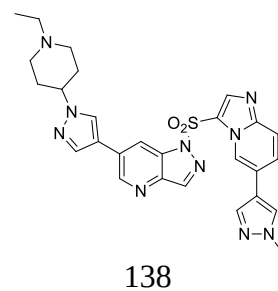
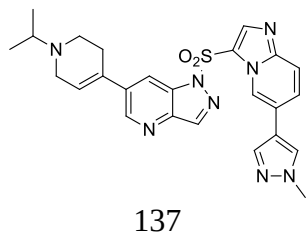
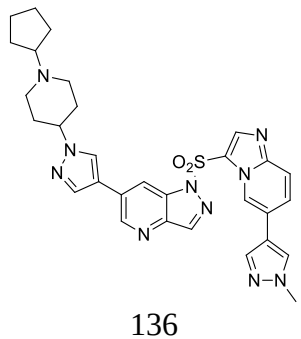
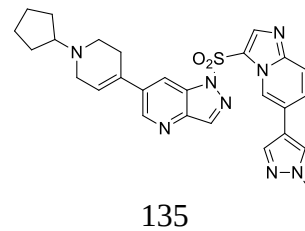
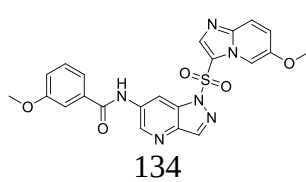
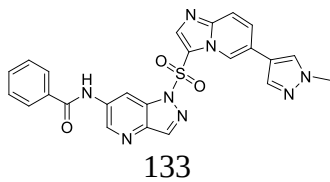
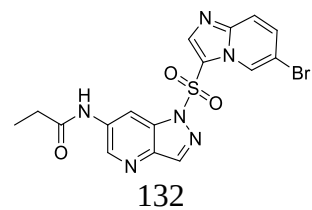
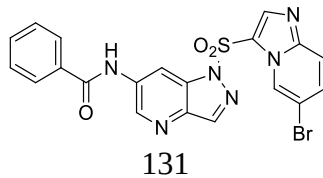
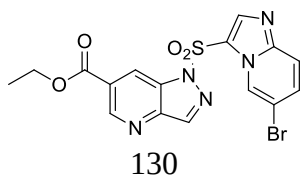
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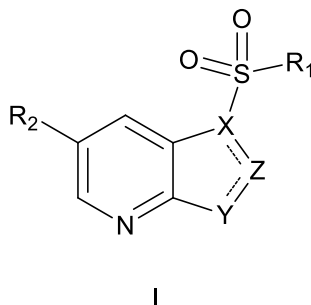


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10. A pharmaceutical composition comprising a prophylactically or therapeutically effective amount of one or more 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof according to claim 1, and a pharmaceutically acceptable excipient.

11. The pharmaceutical composition of claim 10, wherein the 5-member-heterocycle-fused pyridine compound has a structure of Formula (I),



wherein,

X, Y and Z are each independently N or C, at least one of X, Y and Z is N, and Y and Z are unsubstituted; provided that when X is N, Z is N;

— — — represents single bond or double bond, and X, Y and Z abide by valence-bond theory;

R<sub>1</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>), unsubstituted phenyl or phenyl substituted by 1-4 of R<sub>3</sub>, or unsubstituted 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S or 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S substituted by 1-4 of R<sub>4</sub>;

R<sub>2</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is

halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or -NR<sub>c</sub>R<sub>d</sub>-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl;

wherein, R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkoxy-carbonyl-substituted piperidinyl;

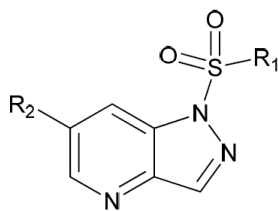
R' is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heterocyclyl;

R'' is C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl; C<sub>1</sub>-C<sub>6</sub> alkoxy-carbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl; or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from the group consisting of halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>a</sub> and R<sub>b</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>c</sub> and R<sub>d</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; or, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl.

12. The pharmaceutical composition of claim 10, wherein the 5-member-heterocycle-fused pyridine compound has a structure of Formula (II),



(II)

wherein:

R<sub>1</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, hydroxyl, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkoxy-carbonyl, -NR<sub>a</sub>R<sub>b</sub>, -C(O)(NR<sub>a</sub>R<sub>b</sub>),

unsubstituted phenyl or phenyl substituted by 1-4 of R<sub>3</sub>, or unsubstituted 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S, or 4- to 7-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S substituted by 1-4 of R<sub>4</sub>;

R<sub>2</sub> is substituted or unsubstituted C<sub>6</sub>-C<sub>20</sub> aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or -NR<sub>c</sub>R<sub>d</sub>-substituted C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> sulfamido, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', morpholinyl, or unsubstituted or R''-substituted piperidinyl;

R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>4</sub> alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or morpholinyl;

R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or unsubstituted or C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl-substituted piperidinyl;

R' is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heterocyclyl;

R'' is C<sub>1</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl; C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl; C<sub>3</sub>-C<sub>6</sub> cycloalkyl carbonyl; or unsubstituted benzoyl or benzoyl substituted by substituent(s) selected from the group consisting of halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, and halogen-substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>a</sub> and R<sub>b</sub> are each independently H, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkyl carbonyl; and

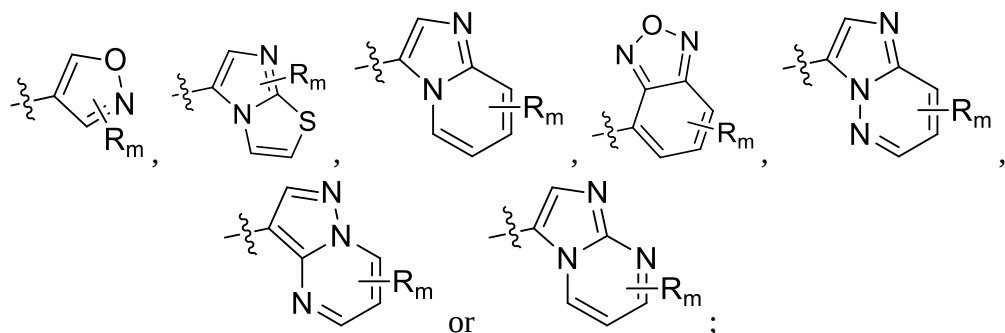
R<sub>c</sub> and R<sub>d</sub> are each independently H or C<sub>1</sub>-C<sub>6</sub> alkyl; or, R<sub>c</sub> and R<sub>d</sub>, together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl.

13. The pharmaceutical composition of claim 10, wherein

X and Z are N, Y is CH;

W and V are independently selected from the group consisting of H, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

R<sub>1</sub> is



$R_m$  is H, halogen, nitro, cyano; unsubstituted or halogen- or morpholinyl-substituted  $C_1$ - $C_4$  alkyl;  $C_1$ - $C_4$  alkoxy;  $C_1$ - $C_4$  alkylcarbonyl;  $C_1$ - $C_4$  alkoxy carbonyl;  $-NR_aR_b$ ;  $-C(O)(NR_aR_b)$ ;  $-OC(O)-R_f$ ; unsubstituted phenyl or phenyl substituted by 1-3 of  $R_3$ ; or unsubstituted 5- to 7-membered heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, O, and S, or 5- to 7-membered heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, O, and S substituted by 1-3 of  $R_4$ , wherein said heteroaryl is selected from the group consisting of furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranlyl, pyridinyl, morpholinyl, oxazinyl, and pyrazinyl;

$R_2$  is cyano;  $C_1$ - $C_4$  alkoxy carbonyl;  $-NR_cR_d$ ; substituted or unsubstituted  $C_6$ - $C_{20}$  aryl; substituted or unsubstituted 5- to 10-membered heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; or substituted or unsubstituted 4- to 10-membered heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, O, and S; wherein, substituent in the substituted group is halogen, nitro, cyano,  $C_1$ - $C_4$  alkylenedioxy, unsubstituted or halogen- or  $-NR_cR_d$ -substituted  $C_1$ - $C_6$  alkyl or  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  sulfamido,  $-NR_aR_b$ ,  $-C(O)R'$ , morpholinyl, morpholinylmethyl, or unsubstituted or  $R''$ -substituted piperidinyl;

$R_3$  is halogen, nitro, cyano,  $C_1$ - $C_2$  alkylenedioxy, unsubstituted or halogen- or morpholinyl-substituted  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $-NR_aR_b$ ,  $-C(O)R'$ , or 4-morpholinyl;

$R_4$  is halogen, nitro, cyano, unsubstituted or halogen-substituted  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $-NR_aR_b$ ,  $-C(O)R'$ , 4-piperidinyl, or 1-*t*-butoxycarbonyl-4-piperidinyl;

$R'$  is  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $-NR_aR_b$ , or 4-methylpiperazinyl;

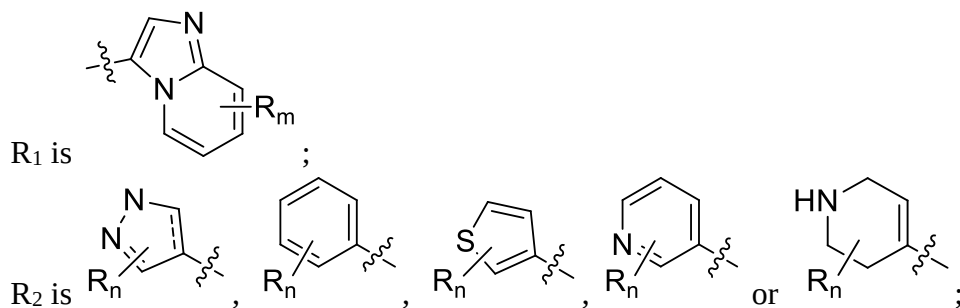
$R''$  is  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_6$  cycloalkyl,  $C_1$ - $C_4$  alkylcarbonyl,  $C_1$ - $C_4$  alkoxy carbonyl,  $C_3$ - $C_6$  cycloalkylcarbonyl, or *p*-trifluoromethylbenzoyl;

$R_a$  and  $R_b$  are each independently H,  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkylcarbonyl;

$R_c$  and  $R_d$  are each independently H or  $C_1$ - $C_6$  alkyl; or,  $R_c$  and  $R_d$ , together with the N atom to which they are attached, form 3- to 7-membered heterocyclyl;

R<sub>f</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl or unsubstituted or halogen- or C<sub>1</sub>-C<sub>6</sub> alkyl-substituted 4- to 7-membered heteroaryl, said 4- to 7-membered heteroaryl is selected from the group consisting of furanyl, pyrrolyl, and thienyl.

14. The pharmaceutical composition of claim 12 or 13, wherein



wherein, R<sub>m</sub> is H, halogen, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, unsubstituted phenyl or phenyl substituted by 1-3 of R<sub>3</sub>, or unsubstituted 5- to 7-membered heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, O, and S, or 5- to 7-membered heteroaryl containing 1-3 heteroatoms selected from the group consisting of N, O, and S substituted by 1-3 of R<sub>4</sub>, wherein said heteroaryl is selected from the group consisting of furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, pyranlyl, pyridinyl, morpholinyl, oxazinyl, and pyrazinyl;

R<sub>n</sub> is H, halogen; nitro; cyano; unsubstituted or halogen-, dimethylamino-, 4-morpholinyl-, 1-aziridinyl-, 1-azetidiny-, 1-tetrahydropyrrolyl-, 1-piperidinyl- or 1-homopiperidinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> sulfamido; -NR<sub>a</sub>R<sub>b</sub>; -C(O)R'; 4-morpholinyl; or unsubstituted or R''-substituted piperidinyl;

R<sub>3</sub> is halogen, nitro, cyano, C<sub>1</sub>-C<sub>2</sub> alkylendioxy, unsubstituted or halogen- or morpholinyl-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', or 4-morpholinyl;

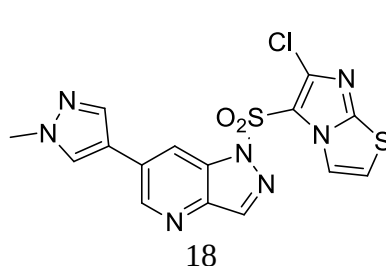
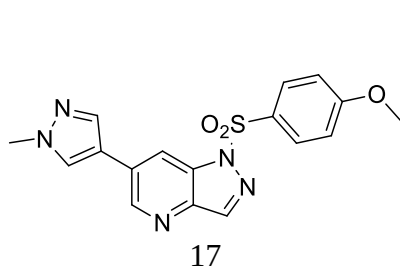
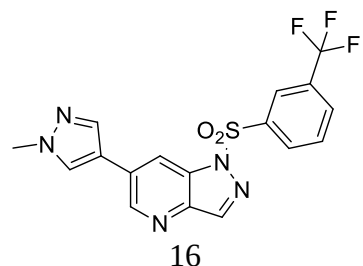
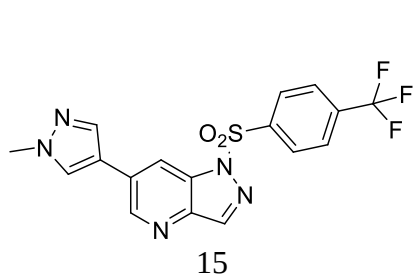
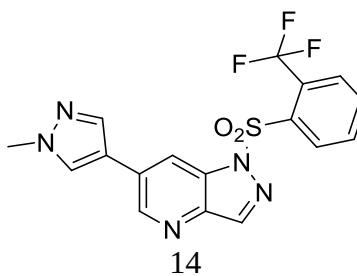
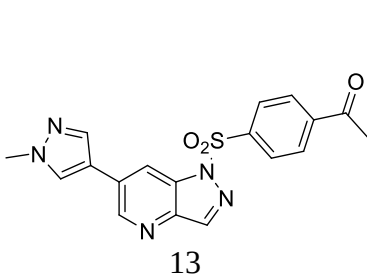
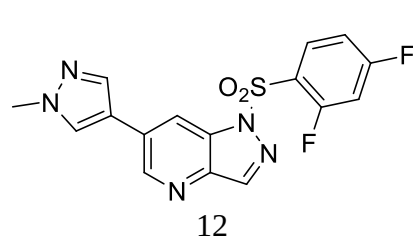
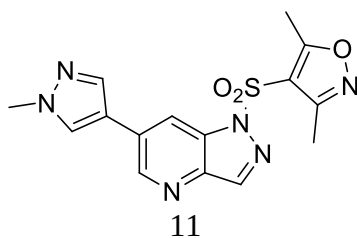
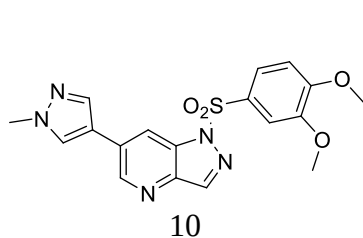
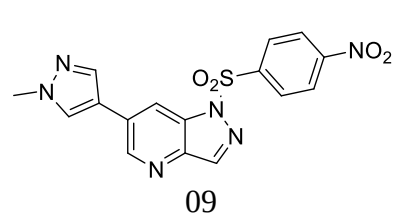
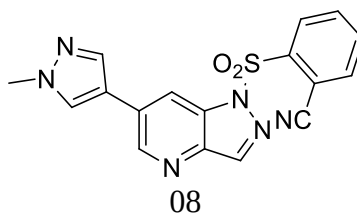
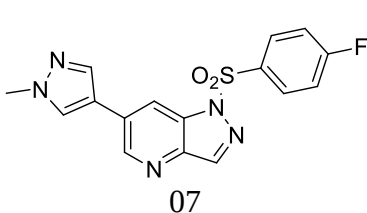
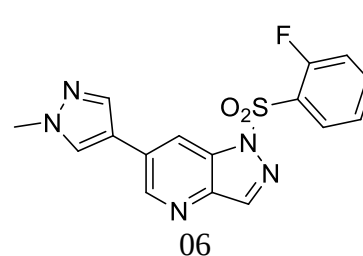
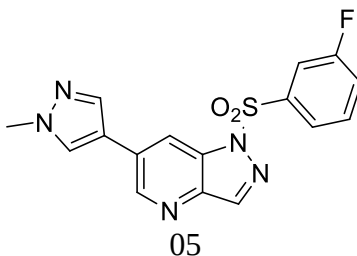
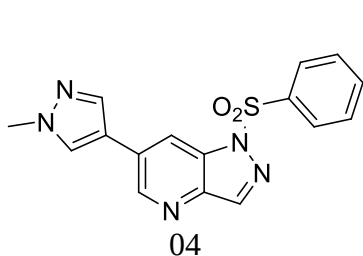
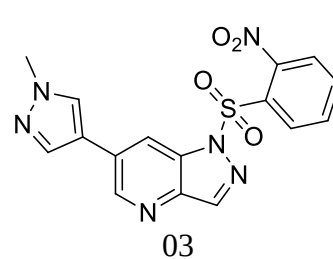
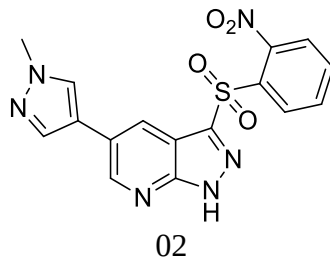
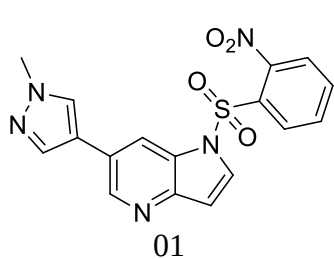
R<sub>4</sub> is halogen, nitro, cyano, unsubstituted or halogen-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, -C(O)R', 4-piperidinyl, or 1-t-butoxycarbonyl-4-piperidinyl;

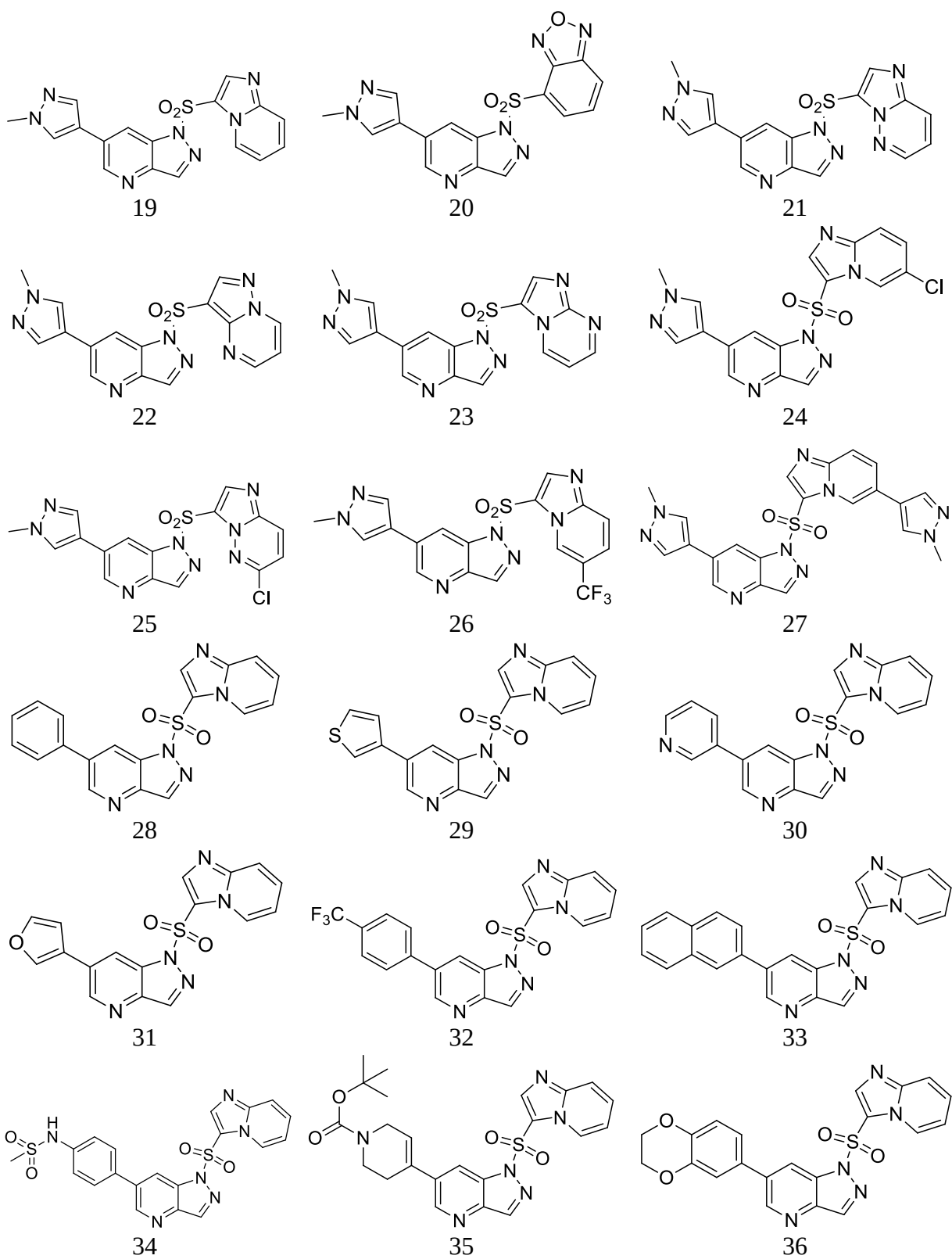
R' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NR<sub>a</sub>R<sub>b</sub>, or 4-methylpiperazinyl;

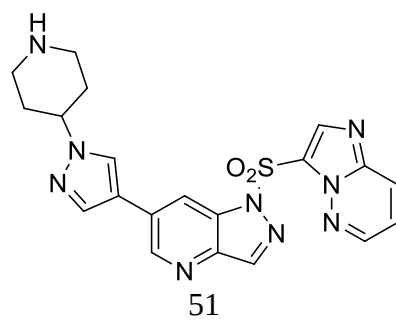
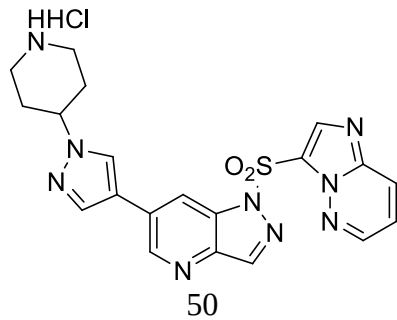
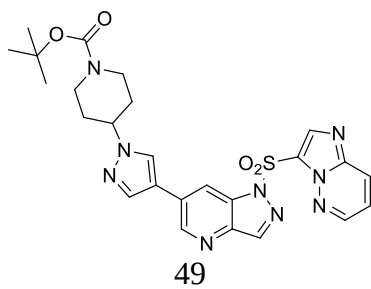
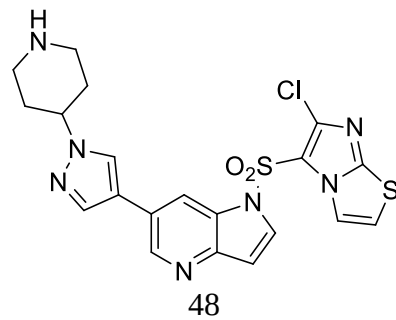
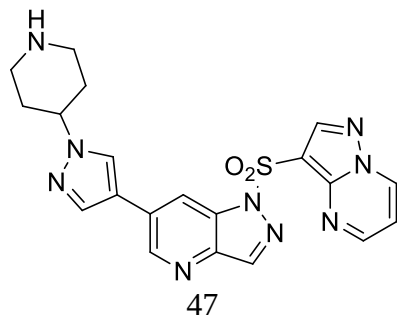
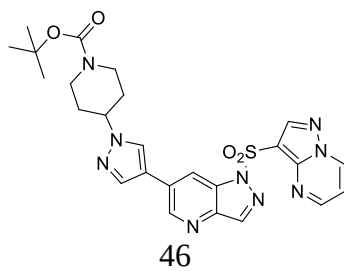
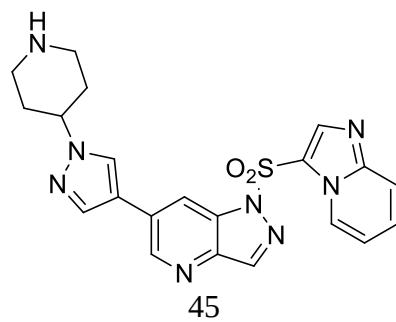
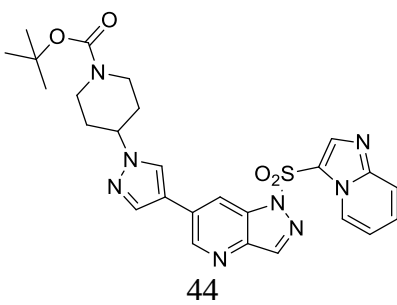
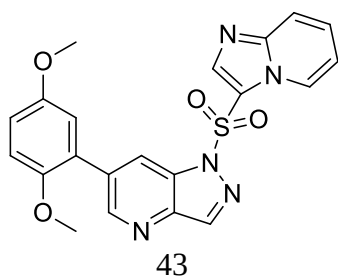
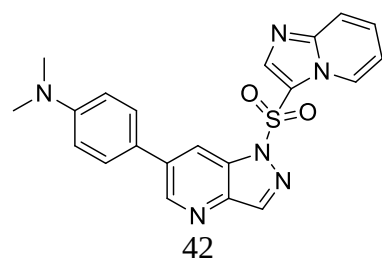
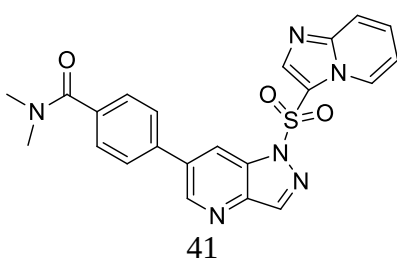
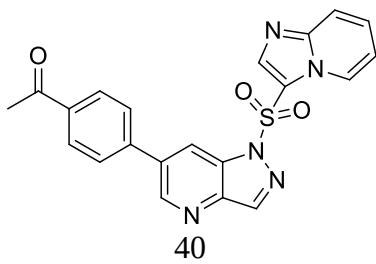
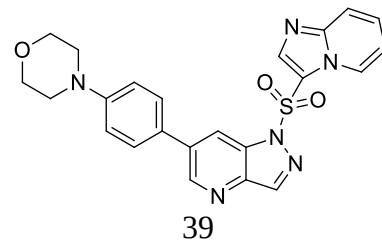
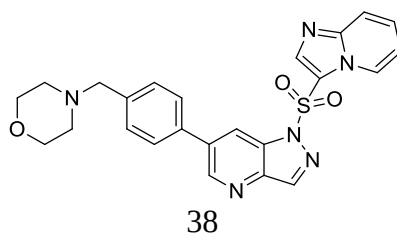
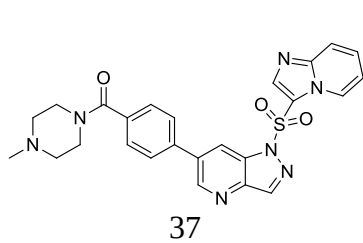
R'' is C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylcarbonyl, or p-trifluoromethylbenzoyl; and

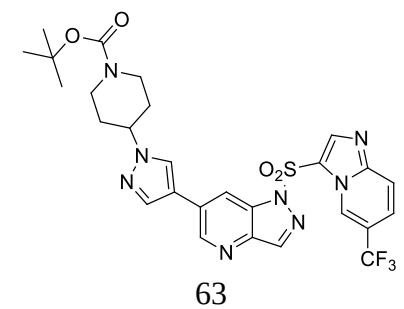
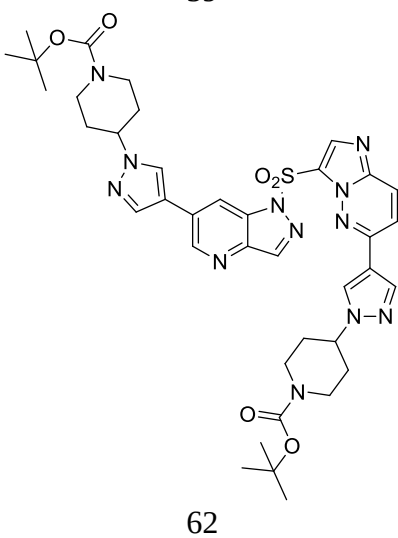
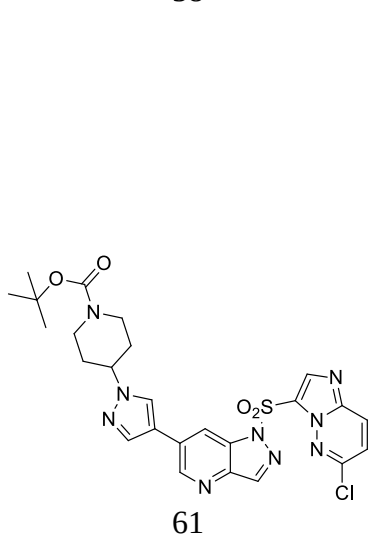
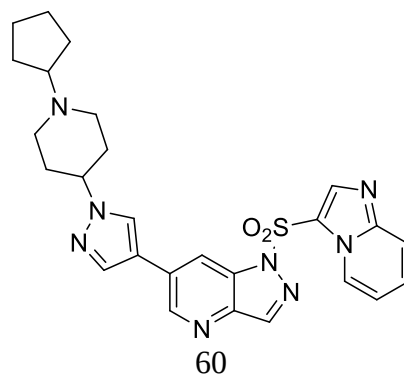
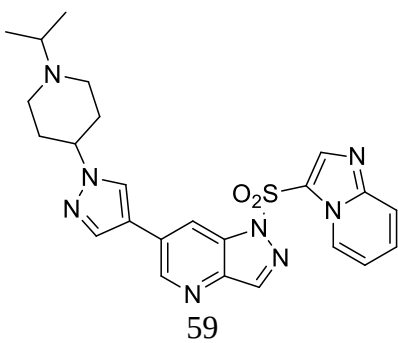
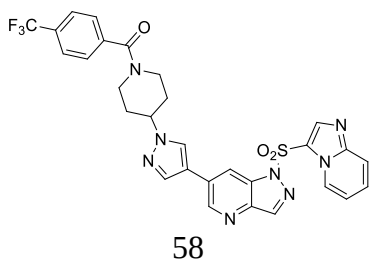
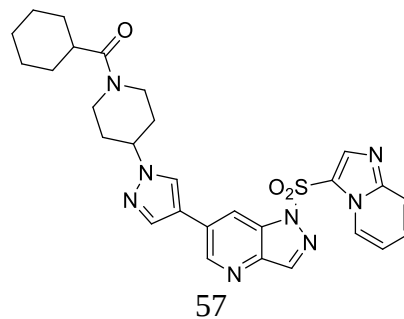
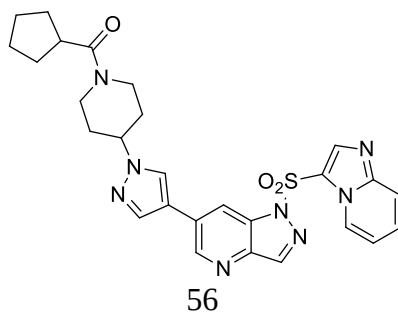
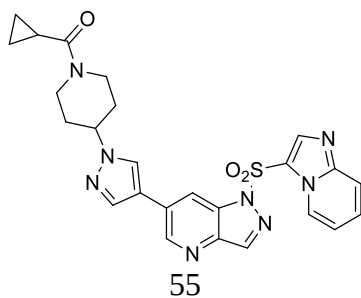
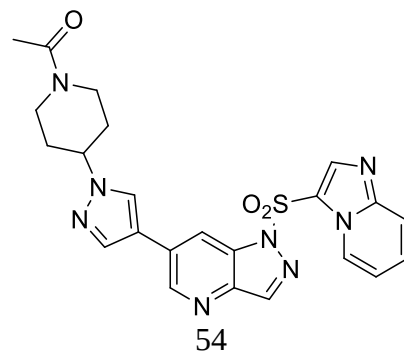
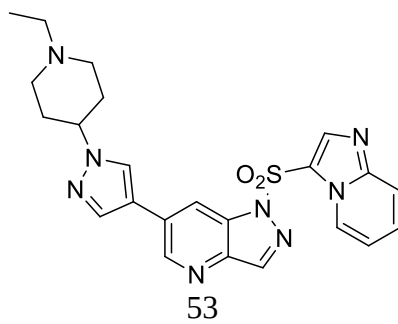
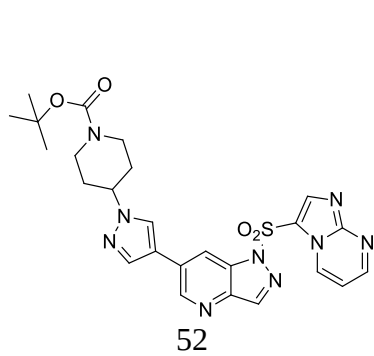
R<sub>a</sub> and R<sub>b</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl.

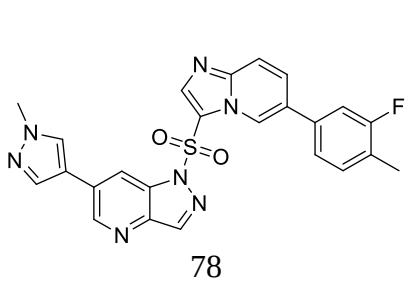
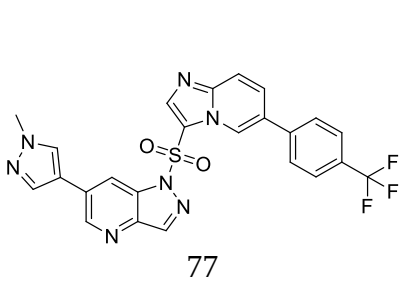
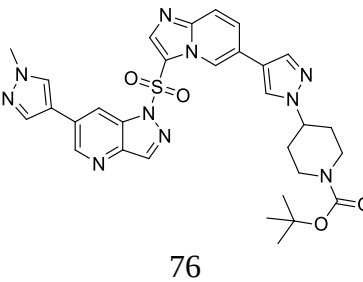
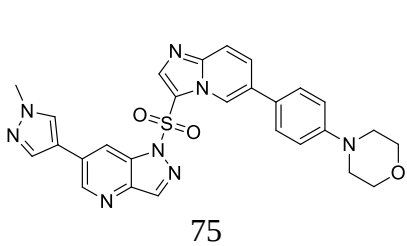
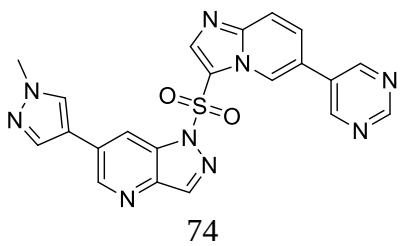
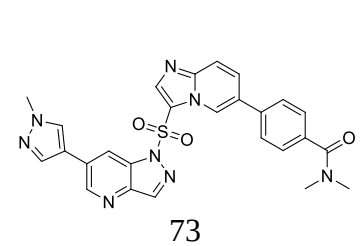
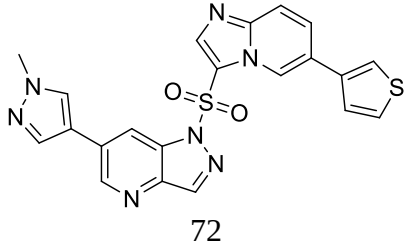
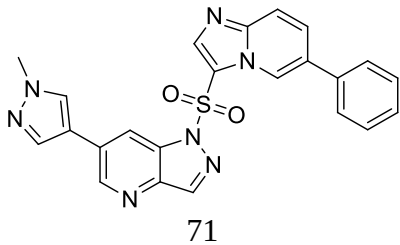
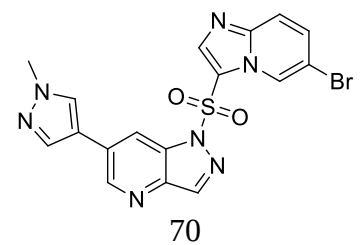
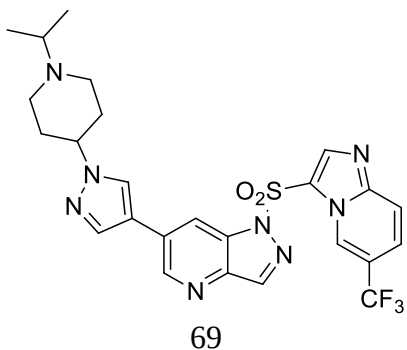
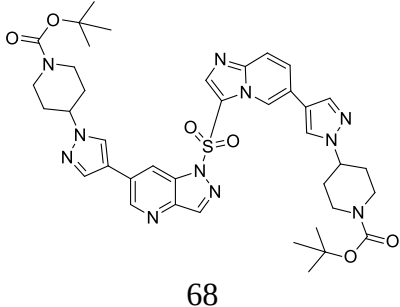
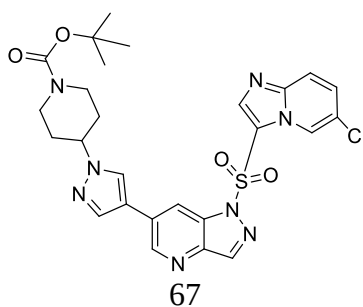
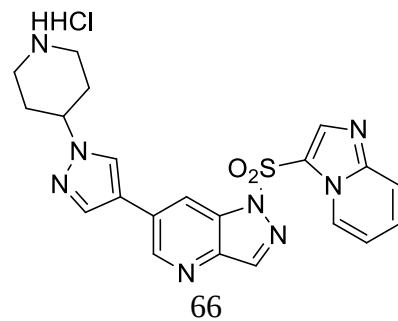
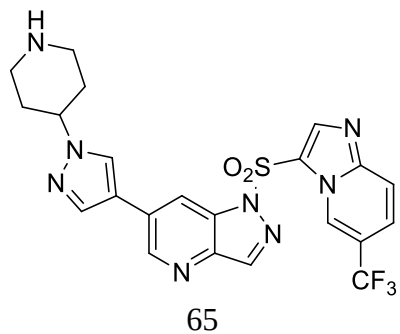
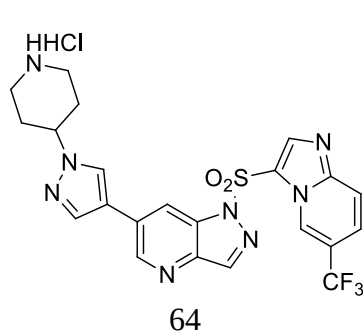
15. The pharmaceutical composition of claim 10, wherein the compound is selected from the group consisting of :

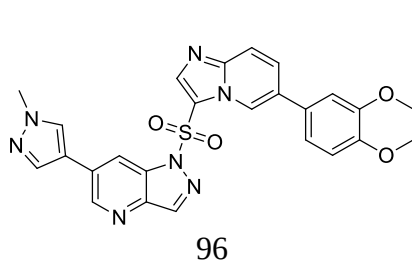
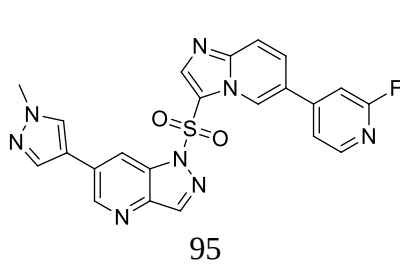
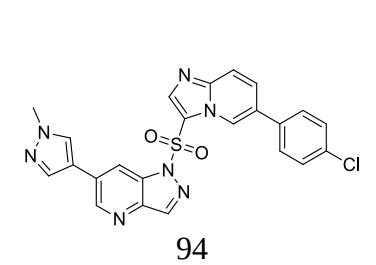
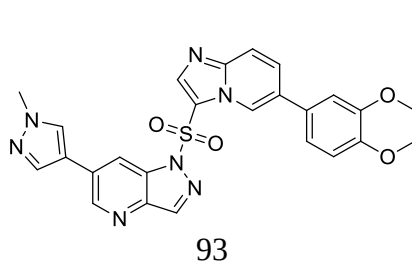
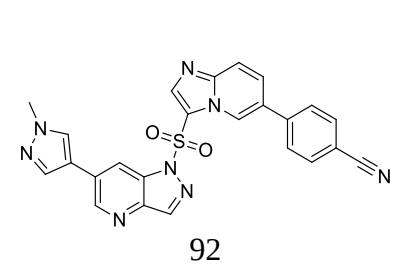
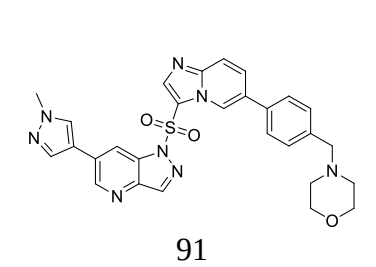
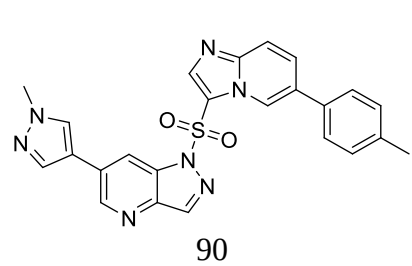
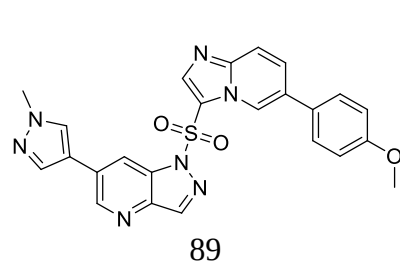
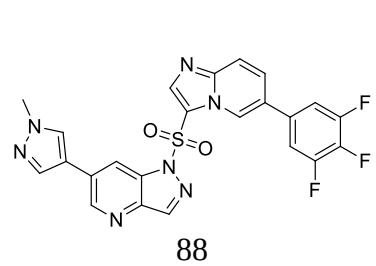
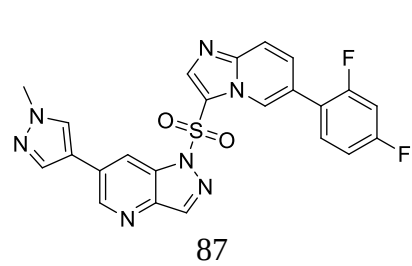
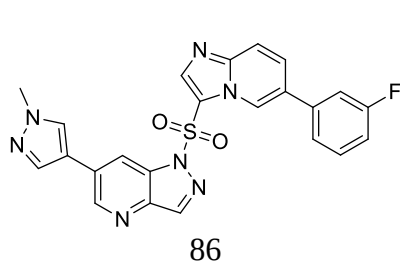
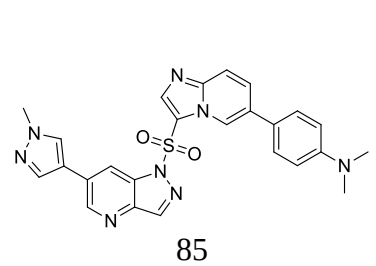
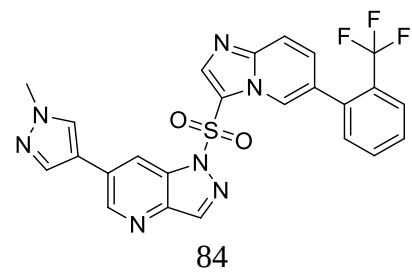
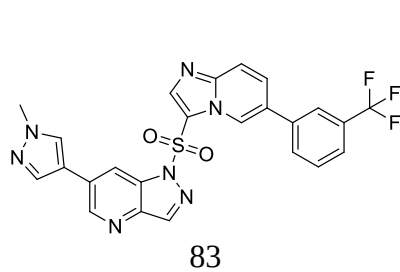
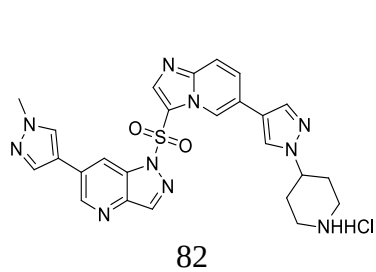
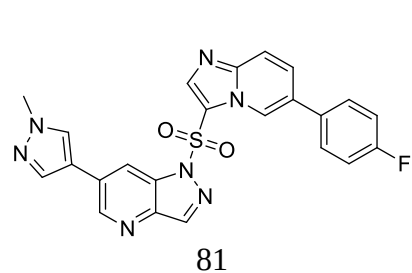
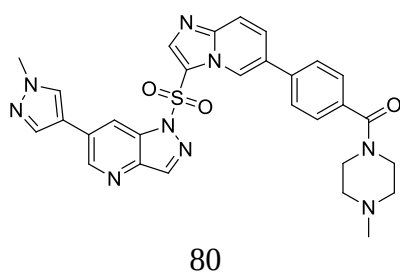
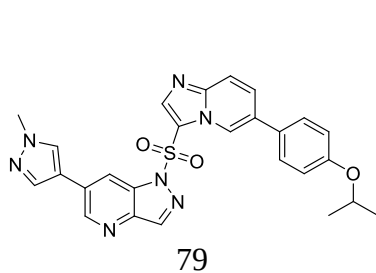


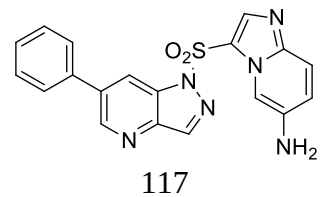
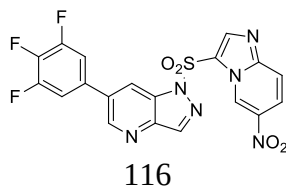
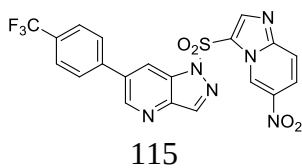
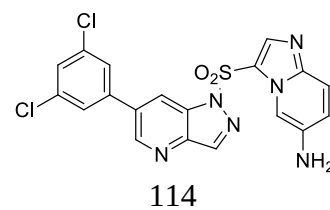
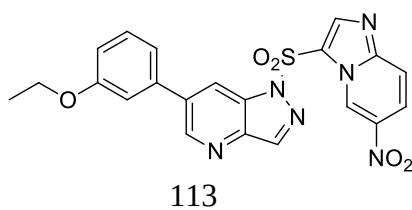
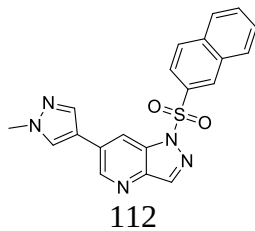
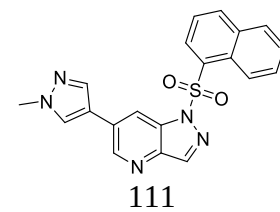
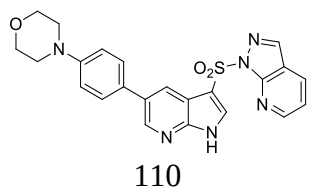
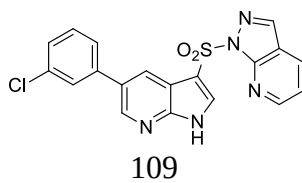
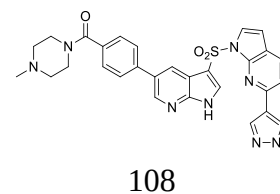
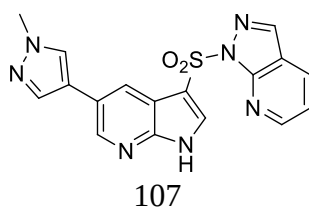
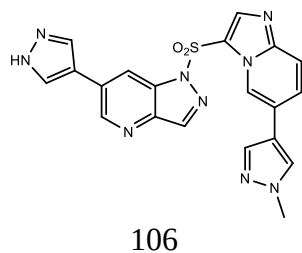
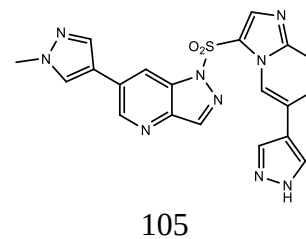
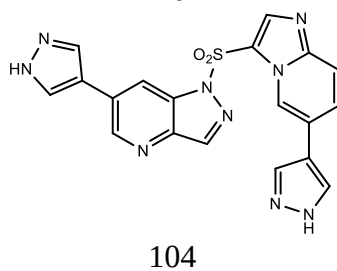
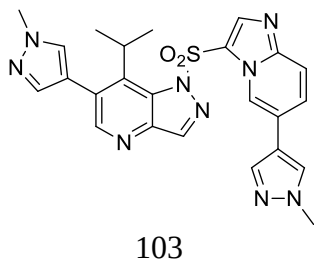
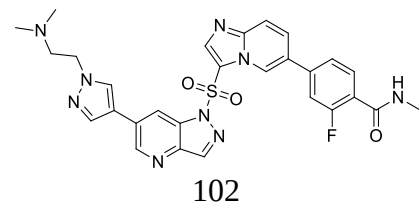
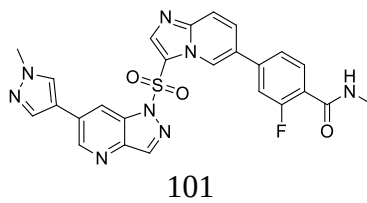
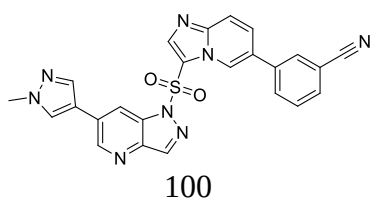
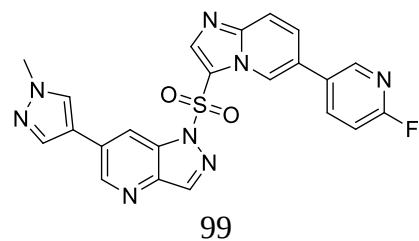
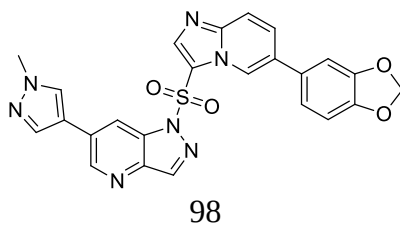
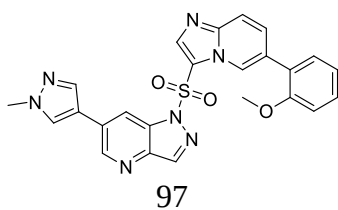


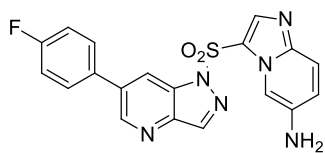




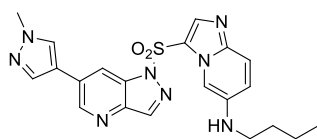




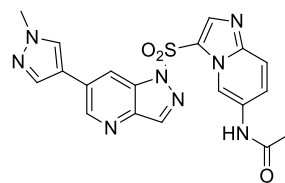




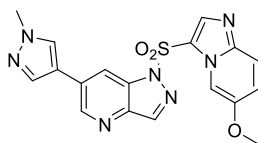
118



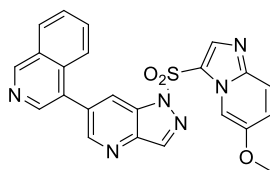
119



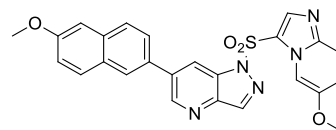
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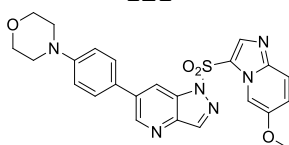
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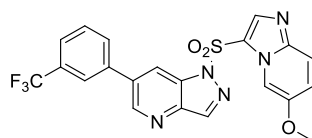
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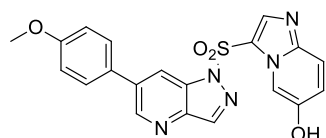
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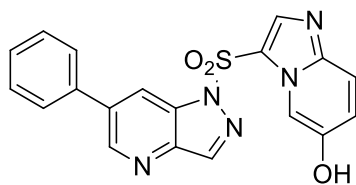
124



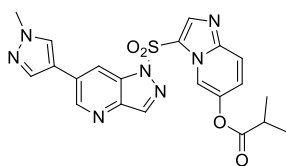
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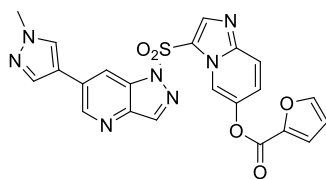
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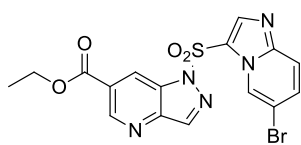
127



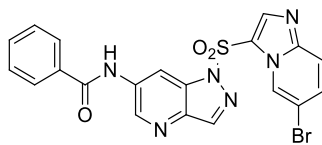
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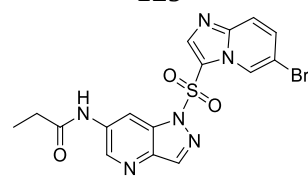
129



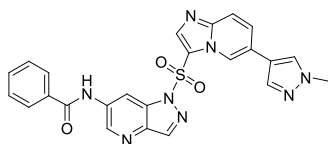
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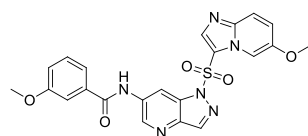
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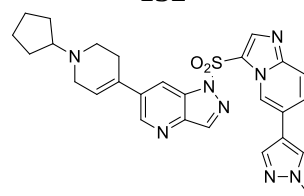
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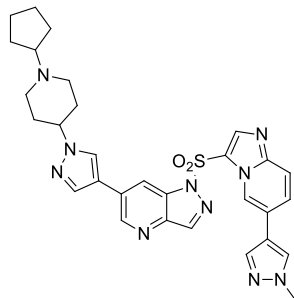
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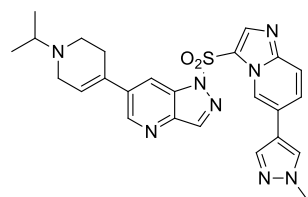
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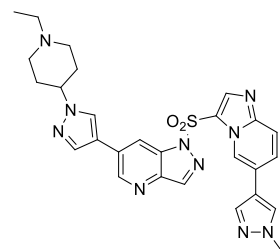
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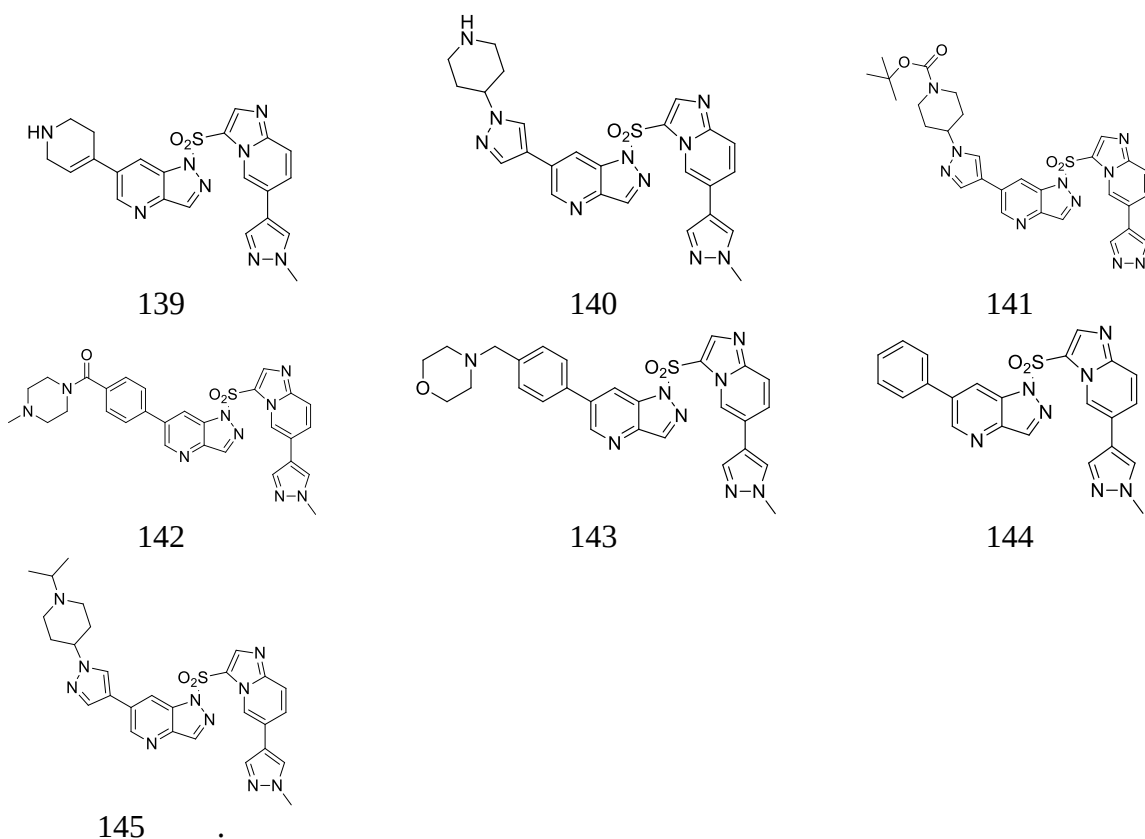
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16. A 5-member-heterocycle-fused pyridine compound, pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof according to any one of claims 1 to 9 or a pharmaceutical composition according to any one of claims 10 to 15 for use in a method of preventing or treating diseases associated with abnormal cell proliferation, morphological change and hyperkinesis related to abnormal protein tyrosine kinase, or diseases related to angiogenesis or metastasis, in a subject in need thereof, said method comprises administering a prophylactically or therapeutically effective amount of said compound or said pharmaceutical composition.

17. The use according to claim 16, wherein the disease associated with abnormal cell proliferation related to abnormal protein tyrosine is a disease associated with abnormal cell proliferation related to abnormal c-Met, and wherein the disease associated with abnormal cell proliferation related to abnormal c-Met is a cancer associated with over-expression or over-activation of c-Met.

18. The use according to claim 17, wherein the cancer associated with over-expression or over-activation of c-Met is selected from the group consisting of liver cancer, bile duct cancer, pancreatic cancer, lung cancer, thyroid cancer, pleural mesothelioma, lung cancer, stomach cancer, breast cancer, colon cancer, prostate cancer, pancreatic cancer, esophageal cancer, ovarian cancer, renal cancer, glioma and melanoma.