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(54) Title: THERAPEUTIC INHIBITORY COMPOUNDS

(57) Abstract: The invention provides compounds of Formula I and Formula II: A-B-C-D-E-F-G-J (I) C-D-E-F-G-J (II) wherein A, B, C, D, E, F, G, and J have any of the values defined in the specification, and salts thereof. The compounds are useful for inhibiting plasma kallikrein, and for treating a disease or condition in an animal where inhibition of plasma kallikrein is indicated.

THERAPEUTIC INHIBITORY COMPOUNDS

Related Applications

This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application Nos. 61/921,995, filed December 30, 2013 and 62/025,203, filed July 16, 2014, which applications are incorporated herein by reference.

Background of the Invention

Modulation of vascular permeability is important in regulating the passage of small molecules or blood cells between blood vessels and surrounding tissues. Vascular permeability can vary with the physiological states of tissues such as during inflammation, changes in blood pressure, and fluctuations in ion and nutrient gradients. The junctions between the endothelial cells that line blood vessels are the immediate controllers of vascular permeability. The strength of these junctions is tightly regulated by the kinin-kallikrein system of polypeptides and enzymes. Abnormalities in the kinin-kallikrein system can lead to a range of pathologies including angioedema, macular edema and brain edema.

The kinin-kallikrein system ("contact system") is responsible for the production of the peptide bradykinin, the proximal molecular mediator of increased vascular permeability (Busse PJ and Buckland MS, *Clin. Exp. Allergy*, 43(4), 385-94, 2013), blood vessel dilation, inflammation (Bjorkqvist J et al., *Thromb. Haemost.* 110(3), 399-407, 2013), and pain (Petho G and Reeh PW, *Physiol. Rev.*, 92(4), 1699-775, 2012). The pathway activation begins with initial generation of zymogen XII (FXII), which is immediately converted into coagulation factor XIIa (FXIIa). FXIIa catalyzes the conversion of prekallikrein to kallikrein, the activated form, which is expressed primarily by hepatocytes in the liver. Activated kallikrein then acts via a positive feedback mechanism to catalyze further conversion of FXII to FXIIa, a process that results in sufficient kallikrein production to drive downstream processes. Kallikrein is a trypsin-like serine protease enzyme. Serine proteases cleave peptide bonds in proteins through a mechanism that involves the binding of a serine residue with the target molecule at the cleavage site. Kallikrein cleaves high molecular weight kinogen (HK) to produce bradykinin. Bradykinin then binds to the bradykinin 2R receptors (BK2R) on endothelial cells to trigger an increase in vascular permeability.

Angioedema is a potentially fatal blood disorder characterized by swelling that may occur in the face, gastrointestinal tract, extremities, genitals and upper airways. Angioedema attacks begin in the deeper layers of the skin and mucous membranes with localized blood vessel dilatation and increased permeability. Symptoms of the disease result from the leakage of plasma from blood vessels into surrounding tissues. Genetic ('hereditary') angioedema ('HAE') attacks result from unregulated activation of the kallikrein system with consequent overproduction of bradykinin and uncontrolled increases in vascular permeability. As vascular permeability rises beyond normal, plasma leaks out of the vasculature into surrounding tissue, causing swelling (Mehta D and Malik AB, *Physiol. Rev.*, 86 (1), 279-367, 2006; Sandoval R et al., *J. Physiol.*, 533(pt 2), 433-45, 2001; Kaplan AP and Greaves MW, Angioedema. *J. Am. Acad. Dermatol.*, 2005).

HAE results from mutations in the genes that code for elements of the coagulation and inflammation pathways. The three forms of HAE are distinguished by their underlying causes and levels of the C1-esterase inhibitor (C1-INH, serpin peptidase inhibitor, clade G, member 1) protein in the blood, which inhibits the

activity of plasma kallikrein. In type I, patients have insufficient levels of functional C1-INH, while type II patients have dysfunctional C1-INH. While type I and II affect men and women at equal rates, type III, which primarily affects women, results from a mutation in coagulation factor XII (Hageman factor; HAE-FXII). The underlying causes of type I and II HAE are autosomal dominant mutations in C1-INH gene (SERPING1 gene) on chromosome 11 (11q12-q13.1).

C1INH accounts for 90% of inhibition of FXIIa and 50% of inhibition of plasma kallikrein (Pixley RA et al., *J. Biol. Chem.*, 260, 1723–9, 1985; Schapira M et al., *Biochemistry*, 20, 2738–43, 1981). In addition, C1-INH also inactivates prekallikrein (Colman RW et al, *Blood*, 65, 311-8, 1985). When C1-INH levels are normal, its activity blocks FXIIa from converting pre-kallikrein to kallikrein and blocks kallikrein's conversion to HK, thus preventing the production of bradykinin and the edemic episodes. When C1-INH levels are low, or levels of dysfunction C1-INH high, this inhibition fails and the pathogenic process ensues.

In addition to HAE, plasma kallikrein may contribute to non-hereditary angioedema, high altitude cerebral edema, cytotoxic cerebral edema, osmotic cerebral edema, diabetic macular edema (DME), clinically significant macular edema, cystoid macular edema (CME, Gao BB, *Nat Med.*, 13(2), 181-8, 2007), retinal edema, radiation induced edema, lymph edema, glioma-associated edema, allergic edema e.g. airflow obstruction in chronic allergic sinusitis or perennial rhinitis. Other disorders of the plasma kallikrein system include retinopathy and diabetic retinopathy (Liu J and Feener EP, *Biol. Chem.* 394(3), 319-28, 2013), proliferative and non-proliferative retinopathy (Liu J et al, *Invest. Ophthalmol. Vis. Sci.*, 54(2), 2013), CME following cataract extraction, CME induced by cryotherapy, CME induced by uveitis, CME following vascular occlusion (e.g., central retinal vein occlusion, branch retinal vein occlusion or hemiretinal vein occlusion), complications related to cataract surgery in diabetic retinopathy, hypertensive retinopathy (JA Phillips et al., *Hypertension*, 53, 175-181, 2009), retinal trauma, dry and wet age-related macular degeneration (AMD), ischemic reperfusion injuries (C Storoni et al., *JPET*, 381, 849-954, 2006), e.g., in a variety of contexts associated with tissue and/or organ transplantation.

In addition, kinin-kallikrein system may contribute to focal cerebral ischemia, damage in surgically-induced brain injury, global cerebral ischemia, spinal cord injury (Radulovic M et al., *J. Neuropathol. Exp. Neurol.*, 72(11), 1072-89, 2013), pain, ischemia, neurological and cognitive deficits, deep vein thrombosis (Bird JE et al., *Thromb. Haemost.* 2012 Jun; 107(6):1141-50), stroke, myocardial infarction (Konings J et al., *Thromb. Res.*, 132(1), 138-42, 2013), acquired angioedema drug-related (ACE-inhibitors), obstructive hydrocephalus, traumatic brain injury, hemorrhagic stroke (e.g., cerebral stroke or subarachnoid stroke), intracerebral hemorrhage, hemorrhagic transformation of ischemic stroke, cerebral trauma associate with injury or surgery, brain aneurysm, arterio-venous malformation, reduction of blood losses during surgical procedures (e.g., cardiothoracic surgery, such as cardiopulmonary bypass or coronary artery bypass grafting), blood coagulation disorders such as thrombosis, itch, disorders with an inflammation component (such as multiple sclerosis; Ma D et al., *Blood* 2013), epilepsy (Simões PS et al., *Neurochem. Int.*, 58(4), 477-82, 2011), encephalitis, Alzheimer's disease (Shropshire TD, et al., *Biol. Chem.* 2013), excessive daytime sleepiness, essential hypertension, increased blood pressure associated with diabetes or hyperlipidemia, renal insufficiency (Martínez-Morillo E, Diamandis A, Diamandis EP, *Clin. Chem. Lab. Med.* 2012 Mar

24;50(5):931-4), chronic kidney disease, heart failure, disorders associated with increased vascular permeability (e.g., increased retinal vascular permeability, increased leg, feet, ankle vascular permeability), cerebral hemorrhage, microalbuminuria (Bodin S et al., *Kidney Int.* 2009 Aug;76(4):395-403), albuminuria and proteinuria, deep vein thrombosis, coagulation from post fibrinolytic treatments, angina, sepsis, arthritis (e.g., rheumatoid arthritis, osteoarthritis, infection arthritis; Dai J et al., *Arthritis Rheum.* 64(11), 3574-82, 2012), lupus, gout, psoriasis, blood loss during cardiopulmonary bypass, inflammatory bowel, diabetes (Feener EP et al., *Thromb. Haemost.*, 110(3), 434-41, 2013), diabetic complications, infectious diseases, astrocyte-activation related diseases (e.g., Alzheimer's disease or multiple sclerosis; Burda JE, *Glia.*, 61(9), 1456-70, 2013), Parkinson's disease, amyotrophic lateral sclerosis, Creutzfeld-Jacob disease, stroke, epilepsy and trauma (e.g., brain trauma), airflow obstruction in acute asthma; serositis associated with systemic lupus erythematosus (SLE) and other diseases.

Current treatments for angioedema, and those under development, target different elements in the HAE pathway. Three classes of therapies are currently available: (a) replacement therapies, (b) selective kallikrein inhibitors and (c) bradykinin receptors antagonists. (A) Replacement therapies have proven useful for both acute attacks, including emergency situations, such as laryngeal edema (Bork K et al., *Transfusion*, 45, 1774–1784, 2005; Bork K and Barnstedt S E, *Arch. Intern. Med.*, 161, 714–718, 2001) and prophylaxis. (B) Selective C1-INH inhibitors inactivate both α-FXIIa and β-FXIIa molecules active early in the HAE pathway that catalyze the production of kallikrein (Muller F and Renne T, *Curr. Opin. Hematol.*, 15, 516–21, 2008; Cugno M et al., *Trends Mol. Med.* 15(2):69-78, 2009). (C) By blocking the bradykinin receptor antagonists prevent bradykinin from activating the vascular permeability pathway and stop the initiation of swelling.

In addition to HAE, plasma kallikrein inhibitors are considered to be useful in the treatment of other edemas such as macular edema and brain edema, and retinopathy, e.g., retinopathy associated with diabetes and/or hypertension. There is evidence that plasma kallikrein inhibitors may also be effective in the treatment of edema formation in diseases, e.g., edema formation related to ischemic reperfusion injuries.

The identification of effective small compounds which potently and specifically inhibit plasma kallikrein is therefore desirable. Preferred compounds should have little affinity for other proteases. They should be well absorbed from the gastrointestinal tract, be sufficiently metabolically stable and possess favorable pharmacokinetic properties. They should be non-toxic and demonstrate few side-effects. Furthermore, the ideal drug candidate will be able to exist in a physical form that is stable, non-hygroscopic and easily formulated.

Design of small molecule drugs targeting plasma kallikrein may yield identification of compounds which target serine proteases similar to kallikrein such as Factor XIa, Factor XIIa, Factor VIIa and related proteases also involved in blood coagulation cascades and vascular permeability pathways.

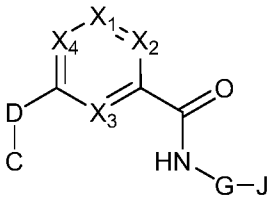
Currently there is a need for agents that are useful for inhibiting plasma kallikrein as well as Factor XIa, Factor XIIa, or Factor VIIa, or other proteases involved in blood coagulation cascades and vascular permeability pathways.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each of the appended claims.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Summary of the Invention

In one aspect of the invention there is provided a compound of Formula IIb:



Formula IIb

wherein:

C is a bicyclic 8-12 membered heteroaryl ring selected from the group consisting of indole, quinoline, isoquinoline, and quinazoline that is optionally substituted with one or more groups independently selected from halo, cyano, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, -$(C_1\text{-}C_6)$alkyl-COOH, $-NR^aR^b$, $S(=O)_2R^e$, and $-C(=O)NR^aR^b$;

D is CH_2;

X_1 is CH and X_4 is N, or X_1 is N and X_4 is CH;

X_2 is CH;

X_3 is CH;

G is CH_2;

J is pyridine, indole, or indazole that is optionally substituted with one or more groups independently selected from halo, $(C_1\text{-}C_6)$alkyl, and $-NR^aR^b$;

each R^a is independently H or $(C_1\text{-}C_6)$alkyl;

each R^b is independently H or $(C_1\text{-}C_6)$alkyl; and

each R^e is independently H or $(C_1\text{-}C_6)$alkyl;

or a salt thereof.

In a further aspect there is provided a compound wherein the compound is:

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide;

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide;

N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide; or

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;

or a salt thereof.

The invention provides a compound of the invention which is a compound of Formula I:

A-B-C-D-E-F-G-J (I)

wherein:

A is a 5 or 6 membered heterocyclic ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$carbocyclyl, $(C_3\text{-}C_6)$ carbocyclyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkanoyl, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, and $(C_2\text{-}C_6)$alkanoyloxy, $-NR^aR^b$, and $-C(=O)NR^aR^b$;

B is absent or is $(C_1\text{-}C_3)$alkyl;

C is phenyl or a 6-membered heteroaryl ring, which phenyl or 6-membered heteroaryl ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$carbocyclyl, $(C_3\text{-}C_6)$ carbocyclyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkanoyl, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_2\text{-}C_6)$alkanoyloxy, $-NR^aR^b$, and $-C(=O)NR^aR^b$;

D is absent, $(C_1\text{-}C_3)$alkyl, halo$(C_1\text{-}C_3)$alkyl, O, S, $S(=O)_2$, or NR^a;

E is a carbocyclic ring or a heterocyclic ring, which carbocyclic ring or a heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$carbocyclyl, $(C_3\text{-}C_6)$ carbocyclyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkanoyl, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_2\text{-}C_6)$alkanoyloxy, $-NR^aR^b$, and $-C(=O)NR^aR^b$;

F is $-S(=O)_2NR^a-$ when E is a 5-membered heteroaryl ring; or F is $-C(=O)-NR^a-$ and C is an unsubstituted phenyl when E is a 5-membered heteroaryl ring; or F is $-C(=O)-NR^a-$ or $-S(=O)_2NR^a-$ when E has any value other than a 5-membered heteroaryl ring;

G is absent or is $(C_1\text{-}C_3)$alkyl that is optionally substituted with one or more groups independently selected from halo, $(C_1\text{-}C_6)$alkoxycarbonyl, and $-C(=O)NR^aR^b$;

J is aryl or heteroaryl, which aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$carbocyclyl, $(C_3\text{-}C_6)$ carbocyclyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkanoyl, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_2\text{-}C_6)$alkanoyloxy, $-C(=O)OR^a$, $-NR^aR^b$, $-C(=O)NR^aR^b$, $-C(=NR^a)NR^aR^b$, and $(C_1\text{-}C_6)$alkyl that is optionally substituted with $-C(=O)OR^a$, $-NR^aR^b$, $-C(=O)NR^aR^b$, or $-C(=NR^a)NR^aR^b$;

R^a is H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkanolyl; and

R^b is H, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkanolyl;

or a salt thereof.

The invention also provides a compound of the invention which is a compound of Formula II:

C-D-E-F-G-J (II)

wherein:

C is a bicyclic 8-12 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, $-NR^aR^b$, and $-C(=O)NR^aR^b$;

D is absent, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, O, S, $S(=O)_2$, or NR^a;

E is a carbocyclic ring or a heterocyclic ring, which carbocyclic ring or a heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, $-NR^aR^b$, and $-C(=O)NR^aR^b$;

F is $-S(=O)_2NR^a-$, $-NR^a S(=O)_2-$, $-NR^a-C(=O)-$, or $-C(=O)-NR^a-$;

G is absent or is (C_1-C_3)alkyl is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, and (C_2-C_6)alkanoyloxy, $-NR^aR^b$, and $-C(=O)NR^aR^b$;

J is bicyclic 8-12 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, $-C(=O)OR^a$, $-NR^aR^b$, $-C(=O)NR^aR^b$, $-C(=NR^a)NR^aR^b$, and (C_1-C_6)alkyl that is optionally substituted with $-C(=O)OR^a$, $-NR^aR^b$, $-C(=O)NR^aR^b$, or $-C(=NR^a)NR^aR^b$;

each R^a is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkyl$S(O)_2$- or $-C(=O)NR^cR^d$, wherein each (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkyl$S(O)_2$- or $-C(=O)NR^cR^d$ is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, and (C_2-C_6)alkanoyloxy, $-NR^aR^b$, and $-C(=O)NR^aR^b$;

each R^b is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, and (C_2-C_6)alkanoyloxy, $-NR^aR^b$, and $-C(=O)NR^aR^b$;

each R^c is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6)

carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, and (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$; and

each R^d is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, and (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$;

or a salt thereof.

The invention also provides a pharmaceutical composition comprising a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, diluent, or carrier.

The invention also provides a method of treating a disease or condition in an animal wherein inhibition of plasma kallikrein is indicated comprising administering a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, to the animal.

The invention also provides a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, for use in medical therapy.

The invention also provides a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a disease or condition wherein inhibition of plasma kallikrein is indicated.

The invention also provides the use of a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, to prepare a medicament for treatment of a disease or condition in an animal wherein inhibition of plasma kallikrein is indicated.

The invention also provides processes and intermediates disclosed herein that are useful for preparing a compound of Formula I or Formula II or a salt thereof.

Compounds of Formula I or Formula II and salts thereof are useful for inhibiting plasma kallikrein.

Detailed Description

The following definitions are included to provide a clear and consistent understanding of the specification and claims. As used herein, the recited terms have the following meanings. All other terms and phrases have their ordinary meanings as one of skill in the art would understand. Such meanings may be obtained by reference to technical dictionaries, such as *Hawley's Condensed Chemical Dictionary* 14th Edition, by R.J. Lewis, John Wiley & Sons, New York, N.Y., 2001.

References in the specification to "one embodiment", "an embodiment", etc., indicate that the embodiment described may include a particular aspect, feature, structure, moiety, or characteristic, but not every embodiment necessarily includes that aspect, feature, structure, moiety, or characteristic. Moreover, such phrases may, but do not necessarily, refer to the same embodiment referred to in other portions of the specification. Further, when a particular aspect, feature, structure, moiety, or characteristic is described in connection with one embodiment, it is within the knowledge of one skilled in the art to affect or connect such

aspect, feature, structure, moiety, or characteristic with other embodiments, whether or not explicitly described, and such combinations are envisaged and are part of the present invention.

The singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a compound" includes a plurality of such compounds, so that a compound X includes a plurality of compounds X. It is further noted that the claims may be drafted to exclude any element, such as any recited definition of a particular variable or other optional elements. As such, this statement is intended to serve as antecedent basis for the use of exclusive terminology, such as "solely", "only", "except", "but not", and the like, in connection with any element or definition described herein, and/or the recitation of claim elements or use of "negative" limitations.

The term "and/or" means any one of the items, any combination of the items, or all of the items with which this term is associated. The phrases "one or more" and "at least one" are readily understood by one of skill in the art, particularly when read in context of its usage. For example, the phrase "one or more" can mean one, two, three, four, five, six, ten, 100, or any upper limit approximately two or ten times higher than a recited lower limit or element (e.g., typically one or two). For example, one or more substituents on a phenyl ring refers to one to five, or one to four, for example if the phenyl ring is currently disubstituted.

The term "about" can refer to a variation of ± 5%, ± 10%, ± 20%, or ± 25% of the value specified. For example, "about 50" percent can in some embodiments carry a variation from 45 to 55 percent. For integer ranges, the term "about" can include one or two integers greater than and/or less than a recited integer at each end of the range. Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percentages, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition, or the embodiment. The term about can also modify the end-points of a recited range as discuss above in this paragraph.

As will be understood by the skilled artisan, all numbers, including those expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth, are approximations and are understood as being optionally modified in all instances by the term "about." These values can vary depending upon the desired properties sought to be obtained by those skilled in the art utilizing the teachings of the descriptions herein. It is also understood that such values inherently contain variability necessarily resulting from the standard deviations found in their respective testing measurements.

One skilled in the art will also readily recognize that where members are grouped together in a common manner, such as in a Markush group, the invention encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group. Additionally, for all purposes, the invention may encompass not only the main group, but also the main group absent one or more of the group members. The invention therefore envisages the explicit exclusion of any one or more of members of a recited group. Accordingly, provisos may apply to any of the disclosed categories or embodiments whereby any one or more of the recited elements, species, or embodiments, may be excluded from such categories or embodiments, for example, for use in an explicit negative limitation.

An "effective amount" refers to an amount effective to treat a disease, disorder, and/or condition, or to bring about a recited effect. For example, an effective amount can be an amount effective to reduce the

progression or severity of the condition or symptoms being treated. Determination of a therapeutically effective amount is well within the capacity of persons skilled in the art. The term "effective amount" can include an amount of a compound described herein, or an amount of a combination of compounds described herein, e.g., that is effective to treat or prevent a disease or disorder, or to treat the symptoms of the disease or disorder, in a host. Thus, an "effective amount" generally means an amount that provides the desired effect.

The terms "treating", "treat" and "treatment" can include (i) preventing a disease, pathologic or medical condition from occurring (e.g., prophylaxis); (ii) inhibiting the disease, pathologic or medical condition or arresting its development; (iii) relieving the disease, pathologic or medical condition; and/or (iv) diminishing symptoms associated with the disease, pathologic or medical condition. Thus, the terms "treat", "treatment", and "treating" can extend to prophylaxis and/or can include prevent, prevention, preventing, lowering, stopping or reversing the progression or severity of the condition or symptoms being treated. As such, the term "treatment" can include medical, therapeutic, and/or prophylactic administration, as appropriate.

The terms "inhibit", "inhibiting", and "inhibition" refer to the slowing, halting, or reversing the growth or progression of a disease, infection, condition, or activity of an enzyme. The inhibition can be greater than about 20%, 40%, 60%, 80%, 90%, 95%, or 99%, for example, compared to the growth or progression that occurs in the absence of the treatment or contacting.

Recursive Substituents. As to any of the formulas described herein or to the groups that contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. Also, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

Selected substituents of the compounds described herein may be present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in a claim of the invention, the total number will be determined as set forth above or as described in this paragraph. In some embodiments, recursive substituents are present only to the extent that the molecular mass of the compound is about 400 to about 1600, about 450 to about 1200, about 500 to about 100, about 500 to about 800. In other embodiments, recursive substituents are present only to the extent that the molecular mass of the compound is less than 2000, less than 1800, less than 1600, less than 1500, less than 1400, less than 1200, less than 1000, less than 900, less than 800, less than 750, less than 700, or less than about 600.

The term "carbocyclyl" used alone or as part of a larger moiety, refers to a saturated, partially unsaturated, or aryl ring system having 3 to 20 carbon atoms. In one embodiment, carbocyclyl includes 3 to 12 carbon atoms (C_3-C_{12}). In another embodiment, carbocyclyl includes C_3-C_8, C_3-C_{10} or C_5-C_{10}. In other embodiment, carbocyclyl, as a monocycle, includes C_3-C_8, C_3-C_6 or C_5-C_6. In another embodiment, carbocyclyl, as a bicycle, includes C_7-C_{12}. In another embodiment, carbocyclyl, as a spiro system, includes C_5-C_{12}. Examples of monocyclic carbocyclyls include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, perdeuteriocyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, phenyl, and cyclododecyl; bicyclic carbocyclyls having 7 to 12 ring atoms include [4,3], [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems, for example bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, naphthalene, and bicyclo[3.2.2]nonane; and spiro carbocyclyls include spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane and spiro[4.5]decane. The term carbocyclyl includes aryl ring systems as defined herein. The term carbocycyl also includes cycloalkyl rings (e.g. saturated or partially unsaturated mono-, bi-, or spiro- carbocycles).

The term "alkyl," as used herein, refers to a saturated linear or branched-chain hydrocarbon radical. A radical as used herein can be a monoradical, diradical, or multiradical, depending on how many substituents the group includes. In one embodiment, the alkyl radical is one to eighteen carbon atoms (C_1-C_{18}). In other embodiments, the alkyl radical is C_1-C_{12}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_5, C_1-C_4 or C_1-C_3. Examples of alkyl groups include methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, heptyl, octyl, nonyl, decyl, undecyl and dodecyl.

The term "alkenyl," as used herein, denotes a linear or branched-chain hydrocarbon radical with at least one carbon-carbon double bond. An alkenyl includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. In one example, the alkenyl radical is two to eighteen carbon atoms (C_2-C_{10}). In other examples, the alkenyl radical is C_2-C_8, C_2-C_6 or C_2-C_3. Examples include, but are not limited to, ethenyl or vinyl ($-CH=CH_2$), prop-1-enyl ($-CH=CHCH_3$), prop-2-enyl ($-CH_2CH=CH_2$), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl and hexa-1,3-dienyl.

The term "alkynyl," as used herein, refers to a linear or branched hydrocarbon radical with at least one carbon-carbon triple bond. In one example, the alkynyl radical is two to eighteen carbon atoms (C_2-C_{10}). In

other examples, the alkynyl radical is C_2-C_8, C_2-C_6 or C_2-C_3. Examples include, but are not limited to, ethynyl (-C≡CH), prop-1-ynyl (-C≡CCH$_3$), prop-2-ynyl (propargyl, -CH$_2$C≡CH), but-1-ynyl, but-2-ynyl and but-3-ynyl.

The term "alkoxy" refers to a linear or branched radical represented by the formula -OR in which R is alkyl, alkenyl, alkynyl or carbocycyl. Alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, and cyclopropoxy.

The term "haloalkyl," as used herein, refers to an alkyl as defined herein that is substituted with one or more (e.g. 1, 2, 3, or 4) halo groups.

The term "aryl" used alone or as part of a larger moiety as in "arylalkyl", "arylalkoxy", or "aryloxyalkyl", refers to a monocyclic, bicyclic or tricyclic, carbon ring system, that includes fused rings, wherein at least one ring in the system is aromatic. The term "aryl" may be used interchangeably with the term "aryl ring". In one embodiment, aryl includes groups having 6-12 carbon atoms. In another embodiment, aryl includes groups having 6-10 carbon atoms. Examples of aryl groups include phenyl, naphthyl, anthracyl, phenanthrenyl, naphthacenyl, 1,2,3,4-tetrahydronaphthalenyl, 1H-indenyl, 2,3-dihydro-1H-indenyl, and the like. A particular aryl is phenyl. In another embodiment aryl includes indanyl, naphthyl, and tetrahydronaphthyl, and the like, where the radical or point of attachment is on an aromatic ring.

The term "heteroaryl" used alone or as part of a larger moiety, e.g., "heteroarylalkyl", or "heteroarylalkoxy", refers to a monocyclic, bicyclic or tricyclic ring system having 5 to 12 ring atoms, wherein at least one ring is aromatic and contains at least one heteroatom. In one embodiment, heteroaryl includes 4-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. In another embodiment, heteroaryl includes 5-6 membered monocyclic aromatic groups where one or more ring atoms is nitrogen, sulfur or oxygen. Examples of heteroaryl groups include thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, tetrazolo[1,5-b]pyridazinyl, imidazol[1,2-a]pyrimidinyl, purinyl, benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl, indolyl, 1,3-thiazol-2-yl, 1,3,4-triazol-5-yl, 1,3-oxazol-2-yl, 1,3,4-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 1H-tetrazol-5-yl, 1,2,3-triazol-5-yl, and pyrid-2-yl N-oxide. The terms "heteroaryl" also includes groups in which a heteroaryl is fused to one or more aryl, carbocyclyl, or heterocyclyl rings, where the radical or point of attachment is on the heteroaryl ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. A heteroaryl group may be mono-, bi- or tri-cyclic.

As used herein, the term "heterocyclyl" refers to a "carbocyclyl" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). In some embodiments, a heterocyclyl refers to a saturated ring system, such as a 3 to 12 membered saturated heterocyclyl ring system. In some embodiments, a heterocyclyl refers to a heteroaryl ring system, such as a 5

to 14 membered heteroaryl ring system. The term heterocyclyl also includes C_3-C_8heterocycloalkyl, which is a saturated or partially unsaturated mono-, bi-, or spiro-ring system comprising 3-8 carbons and one or more (1, 2, 3, or 4) heteroatoms.

In one example, heterocyclyl includes 3-12 ring atoms and includes monocycles, bicycles, tricycles and spiro ring systems, wherein the ring atoms are carbon, and one to five ring atoms is a heteroatom selected from nitrogen, sulfur or oxygen, which is independently optionally substituted by one or more groups. In one example, heterocyclyl includes 1 to 4 heteroatoms. In another example, heterocyclyl includes 3- to 7-membered monocycles having one or more heteroatoms selected from nitrogen, sulfur or oxygen. In another example, heterocyclyl includes 4- to 6-membered monocycles having one or more heteroatoms selected from nitrogen, sulfur or oxygen. In another example, heterocyclyl includes 3-membered monocycles. In another example, heterocyclyl includes 4-membered monocycles. In another example, heterocyclyl includes 5-6 membered monocycles. In one example, the heterocyclyl group includes 0 to 3 double bonds. Any nitrogen or sulfur heteroatom may optionally be oxidized (e.g. NO, SO, SO_2), and any nitrogen heteroatom may optionally be quaternized (e.g. $[NR_4]^+Cl^-$, $[NR_4]^+OH^-$). Example heterocyclyls include oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, dihydro-1H-pyrrolyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, hexahydrothiopyranyl, hexahydropyrimidinyl, oxazinanyl, thiazinanyl, thioxanyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, tetrahydrothiopyranyl, oxazolidinyl, thiazolidinyl, isothiazolidinyl, 1,1-dioxoisothiazolidinonyl, oxazolidinonyl, imidazolidinonyl, 4,5,6,7-tetrahydro[2H]indazolyl, tetrahydrobenzoimidazolyl, 4,5,6,7-tetrahydrobenzo[d]imidazolyl, 1,6-dihydroimidazol[4,5-d]pyrrolo[2,3-b]pyridinyl, thiazinyl, oxazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, thiapyranyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrimidinonyl, pyrimidindionyl, pyrimidin-2,4-dionyl, piperazinonyl, piperazindionyl, pyrazolidinylimidazolinyl, 3-azabicyclo[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 2-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 8-azabicyclo[2.2.2]octanyl, 7-oxabicyclo[2.2.1]heptane, azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, azaspiro[4.5]decanyl, 1-azaspiro[4.5]decan-2-only, azaspiro[5.5]undecanyl, tetrahydroindolyl, octahydroindolyl, tetrahydroisoindolyl, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl and 2-oxopyridin-1(2H)-yl. Examples of 5-membered heterocyclyls containing a sulfur or oxygen atom and one to three nitrogen atoms are thiazolyl, including thiazol-2-yl and thiazol-2-yl N-oxide, thiadiazolyl, including 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl, oxazolyl, for example oxazol-2-yl, and oxadiazolyl, such as 1,3,4-oxadiazol-5-yl, and 1,2,4-oxadiazol-5-yl. Examples of 5-membered ring heterocyclyls containing 2 to 4 nitrogen atoms include imidazolyl, such as imidazol-2-yl; triazolyl, such as 1,3,4-triazol-5-yl; 1,2,3-triazol-5-yl, 1,2,4-triazol-5-yl, and tetrazolyl, such as 1H-tetrazol-5-yl. Example benzo-fused 5-membered

heterocyclyls are benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl. Examples of 6-membered heterocyclyls contain one to three nitrogen atoms and optionally a sulfur or oxygen atom, for example pyridyl, such as pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl; pyrimidyl, such as pyrimid-2-yl and pyrimid-4-yl; triazinyl, such as 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl; pyridazinyl, in particular pyridazin-3-yl, and pyrazinyl. The pyridine N-oxides and pyridazine N-oxides and the pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyridazinyl and the 1,3,4-triazin-2-yl groups, are other example heterocyclyl groups.

As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms but the ring moiety is not aromatic.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase.

When a bond in a compound formula herein is drawn in a non-stereochemical manner (e.g. flat), the atom to which the bond is attached includes all stereochemical possibilities. When a bond in a compound formula herein is drawn in a defined stereochemical manner (e.g. bold, bold-wedge, dashed or dashed-wedge), it is to be understood that the atom to which the stereochemical bond is attached is enriched in the absolute stereoisomer depicted unless otherwise noted. In one embodiment, the compound may be at least 51% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 60% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 80% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 90% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 95 the absolute stereoisomer depicted. In another embodiment, the compound may be at least 99% the absolute stereoisomer depicted.

Specific values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C_1-C_6)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C_3-C_6)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; (C_3-C_6)cycloalkyl(C_1-C_6)alkyl can be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, or 2-cyclohexylethyl; (C_1-C_6)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; (C_2-C_6)alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1- hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, or 5-hexenyl; (C_2-C_6)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1- hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, or 5-hexynyl; (C_1-C_6)alkanoyl can be acetyl, propanoyl or butanoyl; halo(C_1-C_6)alkyl can be iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; halo(C_1-

C_6)alkoxy can be fluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy, or pentafluoroethoxy; hydroxy(C_1-C_6)alkyl can be hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxybutyl, 4-hydroxybutyl, 1-hydroxypentyl, 5-hydroxypentyl, 1-hydroxyhexyl, or 6-hydroxyhexyl; (C_1-C_6)alkoxycarbonyl can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, or hexyloxycarbonyl; (C_2-C_6)alkanoyloxy can be acetoxy, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, or hexanoyloxy; aryl can be phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its *N*-oxide), indolyl, isoquinolyl (or its *N*-oxide) or quinolyl (or its *N*-oxide).

In an aspect of the invention there is provided a compound of Formula I:

A-B-C-D-E-F-G-J (I)

wherein:

A is a 5 or 6 membered heterocyclic ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –$C(=O)NR^aR^b$;

B is absent or is (C_1-C_3)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –$C(=O)NR^aR^b$;

C is phenyl or heteroaryl, which phenyl or heteroaryl is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, (C_1-C_6)alkyl-NR^aR^b, -NR^aR^b, $S(=O)_2R^e$, and –$C(=O)NR^aR^b$;

D is absent, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, alkoxy(C_1-C_3)alkyl, O, S, $S(=O)_2$, -$CH(NR^aR^b)$-, or NR^a;

E is a carbocyclic ring or a heterocyclic ring, which carbocyclic ring or a heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –$C(=O)NR^aR^b$;

F is -$S(=O)_2NR^a$-, -$NR^aS(=O)_2$-, or -NR^a-C(=O)- when E is a 5-membered heteroaryl ring; or F is -C(=O)-NR^a- and C is an unsubstituted phenyl when E is a 5-membered heteroaryl ring; or F

is -S(=O)$_2$NR^a-, -NR^{a}S(=O)$_2$-, -NR^a-C(=O)-, -C(COOR^a)-, -C(CF$_3$)- or -C(=O)-NR^a-; when E has any value other than a 5-membered heteroaryl ring;

G is absent or is (C$_1$-C$_3$)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)carbocyclyl, (C$_3$-C$_6$) carbocyclyl(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxy, halo(C$_1$-C$_6$)alkoxy, (C$_2$-C$_6$)alkenyl, (C$_2$-C$_6$)alkynyl, (C$_1$-C$_6$)alkanoyl, halo(C$_1$-C$_6$)alkyl, hydroxy(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxycarbonyl, and (C$_2$-C$_6$)alkanoyloxy, -NR^{a}R^b, S(=O)$_2$R^e, and –C(=O)NR^{a}R^b;

J is aryl or heteroaryl, which aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)carbocyclyl, (C$_3$-C$_6$)carbocyclyl(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxy, halo(C$_1$-C$_6$)alkoxy, (C$_2$-C$_6$)alkenyl, (C$_2$-C$_6$)alkynyl, (C$_1$-C$_6$)alkanoyl, halo(C$_1$-C$_6$)alkyl, hydroxy(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxycarbonyl, (C$_2$-C$_6$)alkanoyloxy, -C(=O)OR^a, -NR^{a}R^b, –C(=O)NR^{a}R^b, –C(=NR^a)NR^{a}R^b, and (C$_1$-C$_6$)alkyl that is optionally substituted with -C(=O)OR^a, -NR^{a}R^b, –C(=O)NR^{a}R^b, or –C(=NR^a)NR^{a}R^b; or J is –O-NH-C(NH)-NH$_2$;

each R^a is independently H, (C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)carbocyclyl, (C$_1$-C$_6$)alkanoyl, (C$_1$-C$_6$)alkylS(O)$_2$- or –C(=O)NR^{c}R^d, wherein each (C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)carbocyclyl, (C$_1$-C$_6$)alkanoyl, (C$_1$-C$_6$)alkylS(O)$_2$- or –C(=O)NR^{c}R^d is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)carbocyclyl, (C$_3$-C$_6$) carbocyclyl(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxy, halo(C$_1$-C$_6$)alkoxy, (C$_2$-C$_6$)alkenyl, (C$_2$-C$_6$)alkynyl, (C$_1$-C$_6$)alkanoyl, halo(C$_1$-C$_6$)alkyl, hydroxy(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxycarbonyl, and (C$_2$-C$_6$)alkanoyloxy, -NR^{a}R^b, S(=O)$_2$R^e, and –C(=O)NR^{a}R^b;

each R^b is independently H or (C$_1$-C$_6$)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)carbocyclyl, (C$_3$-C$_6$) carbocyclyl(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxy, halo(C$_1$-C$_6$)alkoxy, (C$_2$-C$_6$)alkenyl, (C$_2$-C$_6$)alkynyl, (C$_1$-C$_6$)alkanoyl, halo(C$_1$-C$_6$)alkyl, hydroxy(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxycarbonyl, and (C$_2$-C$_6$)alkanoyloxy, -NR^{a}R^b, S(=O)$_2$R^e, and –C(=O)NR^{a}R^b;

each R^c is independently H or (C$_1$-C$_6$)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)carbocyclyl, (C$_3$-C$_6$) carbocyclyl(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxy, halo(C$_1$-C$_6$)alkoxy, (C$_2$-C$_6$)alkenyl, (C$_2$-C$_6$)alkynyl, (C$_1$-C$_6$)alkanoyl, halo(C$_1$-C$_6$)alkyl, hydroxy(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxycarbonyl, and (C$_2$-C$_6$)alkanoyloxy, -NR^{a}R^b, S(=O)$_2$R^e, and –C(=O)NR^{a}R^b;

each R^d is independently H or (C$_1$-C$_6$)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C$_1$-C$_6$)alkyl, (C$_3$-C$_6$)carbocyclyl, (C$_3$-C$_6$) carbocyclyl(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxy, halo(C$_1$-C$_6$)alkoxy, (C$_2$-C$_6$)alkenyl, (C$_2$-C$_6$)alkynyl, (C$_1$-C$_6$)alkanoyl, halo(C$_1$-C$_6$)alkyl, hydroxy(C$_1$-C$_6$)alkyl, (C$_1$-C$_6$)alkoxycarbonyl, and (C$_2$-C$_6$)alkanoyloxy, -NR^{a}R^b, S(=O)$_2$R^e, and –C(=O)NR^{a}R^b; and

each R^e is independently H or (C$_1$-C$_6$)alkyl;

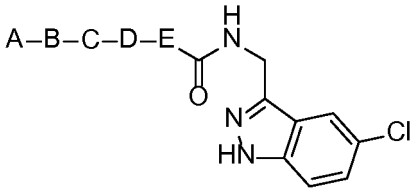
or a salt thereof.

In an embodiment D is hydroxy(C$_1$-C$_6$)alkyl. In an embodiment D is alkoxy(C$_1$-C$_3$)alkyl.

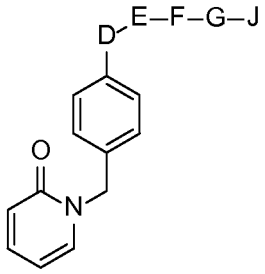
In an embodiment F is -C(COOR^a)-. In an embodiment F is -C(CF$_3$)-.

In an embodiment J is -O-NH-C(NH)-NH_2. In an embodiment J is -C(NH)-NH_2.

In an embodiment, compounds of the invention have the Formula I-aa or I-bb:



I-aa



I-bb

wherein A, B, C, D and E are previously defined. In a particular embodiment, E is phenyl. In a particular embodiment, E is pyridinyl. In a particular embodiment, E is indazolyl. In a particular embodiment, E is piperidinyl. In a particular embodiment, E is pyrazinyl. In a particular embodiment, E is indolyl. In a particular embodiment, E is pyrrolidinyl. In a particular embodiment, E is piperazinyl. In a particular embodiment, E is pyrazolyl. In a particular embodiment, E is 5-oxo-4,5-dihydropyrazinyl.

In another embodiment, the compound of Formula I is

A-B-C-D-E-F-G-J (I)

wherein:

A is a 5 or 6 membered heterocyclic ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, and (C_2-C_6)alkanoyloxy, -NR^aR^b, and –C(=O)NR^aR^b;

B is absent or is (C_1-C_3)alkyl;

C is phenyl or a 6-membered heteroaryl ring, which phenyl or 6-membered heteroaryl ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, (C_1-C_6)alkyl-NR^aR^b, -NR^aR^b, and –C(=O)NR^aR^b;

D is absent, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, O, S, $S(=O)_2$, -CH(NR^aR^b)-, or NR^a;

E is a carbocyclic ring or a heterocyclic ring, which carbocyclic ring or a heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –C(=O)NR^aR^b;

F is -$S(=O)_2NR^a$- when E is a 5-membered heteroaryl ring; or F is -C(=O)-NR^a- and C is an unsubstituted phenyl when E is a 5-membered heteroaryl ring; or F is -C(=O)-NR^a- or -S(=O)2NR^a- when E has any value other than a 5-membered heteroaryl ring;

G is absent or is (C_1-C_3)alkyl that is optionally substituted with one or more groups independently

selected from halo, (C_1-C_6)alkoxycarbonyl, and –C(=O)NR^aR^b;

J is aryl or heteroaryl, which aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -C(=O)OR^a, -NR^aR^b, –C(=O)NR^aR^b, –C(=NR^a)NR^aR^b, and (C_1-C_6)alkyl that is optionally substituted with -C(=O)OR^a, -NR^aR^b, –C(=O)NR^aR^b, or –C(=NR^a)NR^aR^b;

R^a is H, (C_1-C_6)alkyl, or (C_1-C_6)alkanolyl; and

R^b is H, (C_1-C_6)alkyl, or (C_1-C_6)alkanolyl;

or a salt thereof.

A specific value for A is a piperidine, indazole, morpholine, piperazine, oxazolidine, imidazole, or pyrrolidine, that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –C(=O)NR^aR^b.

A specific value for A is a piperidine, indazole, morpholine, piperazine, oxazolidine, imidazole, or pyrrolidine, that is substituted with oxo and that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, and (C_2-C_6)alkanoyloxy, -NR^aR^b, and –C(=O)NR^aR^b.

A specific value for A is a 2-oxopiperidin-1-yl, pyrazole-1-yl, 3-oxomorpholino, 2-oxooxazolidin-3-yl, 2-oxoimidazolidin-1-yl, or 2-oxopyrrolidin-1-yl. In some embodiments, the heterocyclic ring of A is substituted with a fluoro group.

A specific value for B is CH_2.

A specific value for C is phenyl or a 6-membered heteroaryl ring, which phenyl or 6-membered heteroaryl ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –C(=O)NR^aR^b.

A specific value for C is pyridine, pyrimidine, pyrazine, pyridazine, or triazine, wherein any pyridine, pyrimidine, pyrazine, pyridazine, or triazine is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –C(=O)NR^aR^b.

A specific value for C is phenyl or pyridyl where any phenyl or pyridyl is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-

C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –C(=O)NR^aR^b.

A specific value for C is phenyl or pyridyl, where the phenyl or pyridyl is optionally substituted with one or more groups independently selected from halo, hydroxyl, cyano, -NR^aR^b, and –C(=O)NR^aR^b.

A specific value for C is phenyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, cyano, -NR^aR^b, and –C(=O)NR^aR^b.

A specific value for C is pyridyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, cyano, -NR^aR^b, and –C(=O)NR^aR^b.

A specific value for C is phenyl, aminophenyl, fluorophenyl, chlorophenyl, cyanophenyl, aminocarbonylphenyl, hydroxyphenyl, pyridyl, aminopyridyl, or methylsulfonylphenyl.

In another aspect of the invention, there is provided compound of Formula II:

C-D-E-F-G-J (II)

wherein:

C is a bicyclic 8-12 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -(C_1-C_6)alkyl-COOH, -(C_1-C_6)alkyl-CO-(C_1-C_6)alkoxy, -NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b;

or C is a monocyclic carbocyclic ring or a monocyclic heterocyclic ring, which carbocyclic ring or a heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, -(C_1-C_6)alkyl-NR^aR^b, -(C_1-C_6)alkyl-NH-C(O)-NR^aR^b, -(C_1-C_6)alkyl-NH-C(NH)-NR^aR^b, -(C_1-C_6)alkyl-CO-(C_1-C_6)alkoxy, -(C_1-C_6)alkyl-COOH, -(C_1-C_6)alkyl-CO-NR^aR^b, -(C_1-C_6)alkoxy-CO-NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b;

D is absent, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, O, S, $S(=O)_2$, -$CH(NR^aR^b)$-, or NR^a;

E is a carbocyclic ring or a heterocyclic ring, which carbocyclic ring or a heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b;

F is -$S(=O)_2NR^a$-, -NR^a $S(=O)_2$-, -NR^a-C(=O)-, or -C(=O)-NR^a-;

G is absent or is (C_1-C_3)alkyl is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b;

J is bicyclic 8-12 membered heteroaryl ring that is optionally substituted with one or more groups

independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -C(=O)OR^a, -NR^aR^b, –C(=O)NR^aR^b, –C(=NR^a)NR^aR^b, and (C_1-C_6)alkyl that is optionally substituted with -C(=O)OR^a, -NR^aR^b, –C(=O)NR^aR^b, or –C(=NR^a)NR^aR^b;

or J is a monocyclic heterocyclic ring, which heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6)carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, -(C_1-C_6)alkyl-NR^aR^b, -(C_1-C_6)alkyl-NH-C(O)-NR^aR^b, -(C_1-C_6)alkyl-NH-C(NH)-NR^aR^b, -(C_1-C_6)alkyl-CO-(C_1-C_6)alkoxy, -(C_1-C_6)alkyl-COOH, -(C_1-C_6)alkyl-CO-NR^aR^b, -(C_1-C_6)alkoxy-CO-NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b;

each R^a is independently H, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkyl$S(O)_2$- or –C(=O)NR^cR^d, wherein each (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkyl$S(O)_2$- or –C(=O)NR^cR^d is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b;

each R^b is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b;

each R^c is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b; and

each R^d is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b;

each R^e is independently H or (C_1-C_6)alkyl;

or a salt thereof.

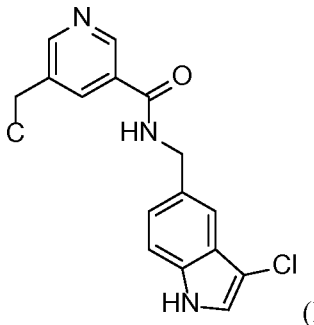
In a particular embodiment, C is a monocyclic carbocyclic ring or a monocyclic heterocyclic ring, which carbocyclic ring or a heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-

C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, -(C_1-C_6)alkyl-NR^aR^b, -(C_1-C_6)alkyl-NH-C(O)-NR^aR^b, -(C_1-C_6)alkyl-NH-C(NH)-NR^aR^b, -(C_1-C_6)alkyl-CO-(C_1-C_6)alkoxy, -(C_1-C_6)alkyl-COOH, -(C_1-C_6)alkyl-CO-NR^aR^b, -(C_1-C_6)alkoxy-CO-NR^aR^b, $S(=O)_2R^e$, and –C(=O)NR^aR^b.

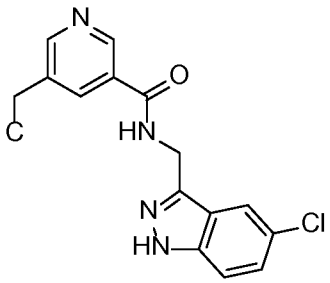
In a particular embodiment, C is pyridyl. In a particular embodiment, C is phenyl. In another particular embodiment, C is quinoline or quinoline substituted with halo, such as fluoro, or a (C_1-C_6)alkyl, such as methyl.

In a particular embodiment, C is substituted with -(C_1-C_6)alkyl-NR^aR^b. In a particular embodiment, C is substituted with aminomethyl. In a particular embodiment, C is substituted with -(C_1-C_6)alkyl-NR^aR^b. In a particular embodiment, C is substituted with acetamidomethyl. In a particular embodiment, C is substituted with -(C_1-C_6)alkyl-CO-NR^aR^b. In a particular embodiment, C is substituted with 2-amino-2-oxoethyl. In a particular embodiment, C is substituted with 3-amino-3-oxopropyl. In a particular embodiment, C is substituted with -(C_1-C_6)alkyl-CO-(C_1-C_6)alkoxy. In a particular embodiment, C is substituted with –CH_2-COO-Me. In a particular embodiment, C is substituted with –$(CH_2)_2$-COO-Me. In a particular embodiment, C is substituted with -(C_1-C_6)alkyl-NH-C(O)-NR^aR^b. In a particular embodiment, C is substituted with –CH_2-NH-CO-NH_2. In a particular embodiment, C is substituted with -(C_1-C_6)alkoxy-CO-NR^aR^b. In a particular embodiment, C is substituted with –O-CH_2-CO-NH_2. In a particular embodiment, C is substituted with -(C_1-C_6)alkyl-NR^aR^b. In a particular embodiment, C is substituted with methylacetamidomethyl. In a particular embodiment, C is substituted with 1-acetamidoethyl.

In a particular embodiment, there is provided a compound of Formula II-aa or II-bb:



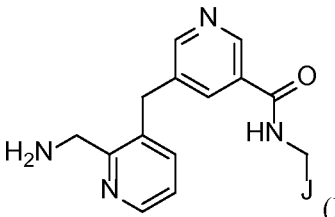
(II-aa)



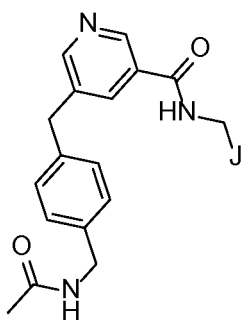
(II-bb)

wherein C is as defined herein for Formula II. In a particular embodiment, C phenyl, optionally substituted as defined herein for Formula II. In another embodiment, C is pyridyl, optionally substituted as defined herein for Formula II.

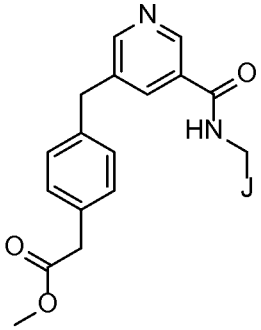
In another embodiment, there is provided a compound of Formula II-cc through II-nn:



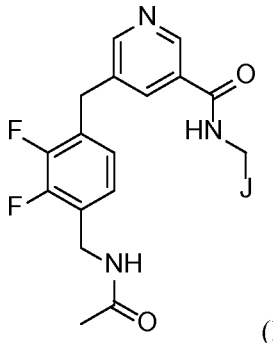
(II-cc)

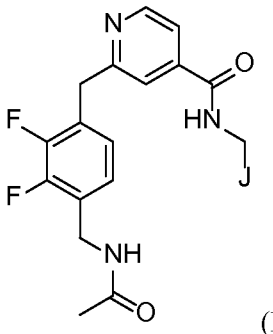


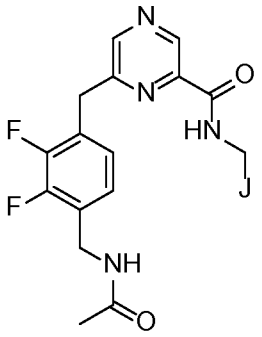
(II-dd)

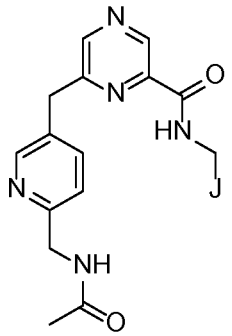


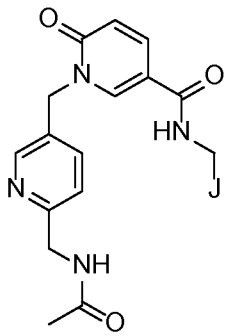
(II-ee)

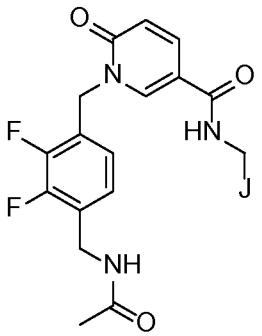

(II-ff)

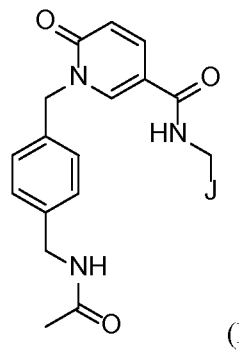

(II-gg)

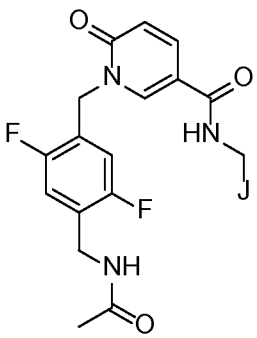

(II-hh)

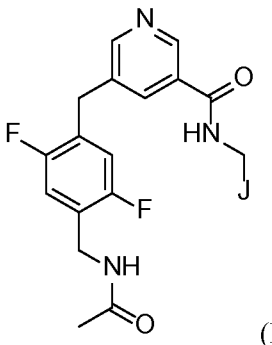

(II-ii)


(II-jj)


(II-kk)


(II-ll)


(II-mm)


(II-nn)

wherein J is as defined herein for Formula II. In a particular embodiment, J is indole. In a particular embodiment, J is 3-chloro-6-fluoro-1H-indol-5-yl. In a particular embodiment, J is 3-chloro-1H-indol-5-yl. In a particular embodiment, J is indazolyl. In a particular embodiment, J is 5-chloro-1H-indazol-3-yl. In a particular embodiment, J is pyrrolo[2,3-b]pyridinyl. In a particular embodiment, J is 3-chloro-1H-pyrrolo [2,3-b]pyridin-5-yl. In a particular embodiment, J is a monocyclic heterocyclic ring. In a particular embodiment, J is an amino-dimethylpyridinyl group such as 6-amino-2,4-dimethylpyridin-3-yl.

In a particular embodiment, there is provided a compound of Formula II:

C-D-E-F-G-J (II)

wherein:

C is a bicyclic 8-12 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$;

D is absent, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, O, S, $S(=O)_2$, -$CH(NR^aR^b)$-, or NR^a;

E is a carbocyclic ring or a heterocyclic ring, which carbocyclic ring or a heterocyclic ring is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$;

F is -$S(=O)_2NR^a$-, -$NR^aS(=O)_2$-, -NR^a-C(=O)-, or -C(=O)-NR^a-;

G is absent or is (C_1-C_3)alkyl is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$;

J is bicyclic 8-12 membered heteroaryl ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -$C(=O)OR^a$, -NR^aR^b, –$C(=O)NR^aR^b$, –$C(=NR^a)NR^aR^b$, and (C_1-C_6)alkyl that is optionally substituted with -$C(=O)OR^a$, -NR^aR^b, –$C(=O)NR^aR^b$, or –$C(=NR^a)NR^aR^b$;

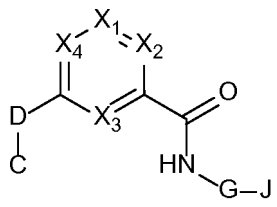
each R^a is independently H, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkylS$(O)_2$- or –$C(=O)NR^cR^d$, wherein each (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkylS$(O)_2$- or –$C(=O)NR^cR^d$ is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$;

each R^b is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$;

each R^c is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$; and

each R^d is independently H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$; or a salt thereof.

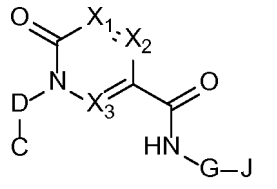
A specific compound of Formula II is a compound of Formula IIb:



Formula IIb

wherein each X_1, X_2, X_3 and X_4 is independently CH or N; and G is $(C_1$-$C_3)$alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$carbocyclyl, $(C_3$-$C_6)$ carbocyclyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$alkanoyl, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl, $(C_2$-$C_6)$alkanoyloxy, $-NR^aR^b$, $S(=O)_2R^e$, and $-C(=O)NR^aR^b$.

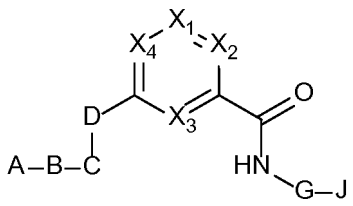
A specific compound of Formula II is a compound of Formula IIc:



Formula IIc

wherein each of X_1, X_2, X_3 and X_4 is independently CH or N; and G is $(C_1$-$C_3)$alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$carbocyclyl, $(C_3$-$C_6)$ carbocyclyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$alkanoyl, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl, $(C_2$-$C_6)$alkanoyloxy, $-NR^aR^b$, $S(=O)_2R^e$, and $-C(=O)NR^aR^b$.

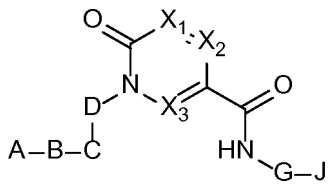
A specific compound of Formula I is a compound of Formula Ib:



Formula Ib

wherein each X_1, X_2, X_3 and X_4 is independently CH or N; and G is $(C_1$-$C_3)$alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$carbocyclyl, $(C_3$-$C_6)$ carbocyclyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$alkanoyl, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl, $(C_2$-$C_6)$alkanoyloxy, $-NR^aR^b$, $S(=O)_2R^e$, and $-C(=O)NR^aR^b$.

A specific compound of Formula I is a compound of Formula Ic:



Formula Ic

wherein each of X_1, X_2, X_3 and X_4 is independently CH or N; and G is $(C_1$-$C_3)$alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$carbocyclyl, $(C_3$-$C_6)$ carbocyclyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_2$-

C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, $S(=O)_2R^e$, and –$C(=O)NR^aR^b$.

A specific value for C is a quinoline that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$.

A specific value for C is a 6-quinoline that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$.

A specific value for C is a 2-methyl-6-quiolinyl.

A specific value for D is (C_1-C_3)alkyl. Another specific value for D is methylene.

A specific value for E is a carbocyclic ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$.

A specific value for E is a heterocyclic ring that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$;

A specific value for E is pyrazole, pyridine, indole, phenyl, morpholine, pyrimidine, pyrazine, pyradizine, 2-oxooxazolidine, pyrrolidine, 2-oxopyrrolidine, piperazine, oxopiperazine, oxopyridine, oxopyrimidine, oxopiperidine, oxomorpholine, azaspiro[3,4]octane, 5-thia-2-azaspiro[3,4]octane, hydroxypyridine, indazole, 1H-pyrrolo[2,3-b]pyridine, or hydroxypyrimidine, wherein E is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –$C(=O)NR^aR^b$.

A specific value for E is pyrazole, pyridine, or phenyl.

A specific value for E is pyrazole.

A specific value for E is pyridine.

A specific value for F is -$S(=O)_2NR^a$-.

A specific value for F is -NR^a $S(=O)_2$-.

A specific value for F is -NR^a-C(=O)-.

A specific value for F is -C(=O)-NR^a-.

A specific value for G is (C_1-C_3)alkyl optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, oxo, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b, and –C(=O)NR^aR^b.

Another specific value for G is methylene.

A specific value for J is aryl. Another specific value for J is heteroaryl. The aryl or heteroaryl can be substituted. In one embodiment, the substituents are one or more halo, amino, or methyl groups, or a combination thereof.

Another specific value for J is 8-10 membered heteroaryl ring. The heteroaryl ring can be substituted, for example, with one or more halo, amino, or methyl groups, or a combination thereof.

Another specific value for J is monocyclic heterocyclic ring. In one embodiment, the monocyclic heterocyclic ring is substituted with one or more halo, amino, or methyl groups, or a combination thereof.

A specific value for J is indazole that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -C(=O)OR^a, -NR^aR^b, –C(=O)NR^aR^b, –C(=NR^a)NR^aR^b, and (C_1-C_6)alkyl that is optionally substituted with -C(=O)OR^a, -NR^aR^b, –C(=O)NR^aR^b, or –C(=NR^a)NR^aR^b.

A specific value for J is indazole-3-yl that is optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b,–C(=O)NR^aR^b, –C(=NR^a)NR^aR^b, and (C_1-C_6)alkyl that is optionally substituted with NR^aR^b.

A specific value for J is chloro-indazole-3-yl. Another specific value for J is 5-chloro-indazole-3-yl.

Specific values for J also include indole, pyridine, azaindole, quinoline, or isoquinoline, each optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -C(=O)OR^a, -NR^aR^b, –C(=O)NR^aR^b, –C(=NR^a)NR^aR^b, and (C_1-C_6)alkyl that is optionally substituted with -C(=O)OR^a, -NR^aR^b, –C(=O)NR^aR^b, or –C(=NR^a)NR^aR^b.

Specific values for J further include 1-aminoisoquinolin-6-yl, 3-chloro-6-fluoro-1H-indol-5-yl, 6-amino-2,4-dimethylpyridin-3-yl, 3-chloro-4-fluoro-1H-indol-5-yl, or 3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl, which groups can be optionally substituted with one or more groups independently selected from halo, hydroxyl, nitro, cyano, (C_1-C_6)alkyl, (C_3-C_6)carbocyclyl, (C_3-C_6) carbocyclyl(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkanoyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl, (C_2-C_6)alkanoyloxy, -NR^aR^b,–C(=O)NR^aR^b, –C(=NR^a)NR^aR^b, and (C_1-C_6)alkyl that is optionally substituted with -C(=O)OR^a, NR^aR^b, or –C(=O)NR^aR^b.

In one embodiment, J is isoquinoline. The isoquinoline can be optionally substituted as described above. In one specific embodiment, J is 1-aminoisoquinolin-6-yl.

A specific value for R^a or R^b is H. Another specific value for R^a or R^b is acetyl. Another specific value for R^a or R^b is 2-hydroxy-acetyl. Another specific value for R^a or R^b is 2-amino-acetyl. Another specific value for R^a or R^b is methoxyformyl. Another specific value for R^a or R^b is cyclopropylformyl. Another specific value for R^a or R^b is cyclopropyl.

Specific values for X_1, X_2, X_3 and X_4 are CH.

Specific values for X_1 is N, and X_2, X_3 and X_4 are CH.

Specific values for X_1 and X_3 are N, and X_2 and X_4 are CH.

Specific values for X_1 and X_4 are N, and X_2 and X_3 are CH.

Specific values for X_1 and X_2 are N, and X_3 and X_4 are CH.

A specific compound of the invention can be selected from **Table 1**.

Specific compound of the invention can also be selected from:

N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-2-sulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)picolinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-2-carboxamide;

methyl 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetate;

2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetic acid;

N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)isonicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)- benzenesulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)pyridine-3-sulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(methyl(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)-benzenesulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)morpholine-2-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrimidine-2-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrazine-2-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-4-sulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-oxo-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)oxazolidine-5-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)- pyrrolidine-3-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrrolidine-3-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(methyl(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)-amino)benzamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-(methyl(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)-acetamido)nicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-6-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)-acetamido)picolinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-2-sulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)pyridine-4-sulfonamide;

N-(3-(N-((5-chloro-1H-indazol-3-yl)methyl)sulfamoyl)phenyl)-N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)pyridine-2-sulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)pyridine-4-sulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrimidine-4-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrimidine-4-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrrolidine-1-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrrolidine-1-sulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrrolidine-3-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-oxo-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)oxazolidine-5-sulfonamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-1-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)morpholine-4-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-methyl-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1-carboxamide;

4-acetyl-N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-oxo-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-methyl-3-oxo-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)morpholine-2-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)piperidine-3-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-4-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)-morpholine-2-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-5-azaspiro[3.4]octane-2-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-5-thia-2-azaspiro[3.4]octane-8-carboxamide 5,5-dioxide;

2-(5-chloro-1H-indazol-3-yl)-2-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)acetic acid;

methyl 2-(5-chloro-1H-indazol-3-yl)-2-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)acetate;

N-(2-amino-1-(5-chloro-1H-indazol-3-yl)-2-oxoethyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide;

3-(5-chloro-1H-indazol-3-yl)-3-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)propanoic acid;

methyl 3-(5-chloro-1H-indazol-3-yl)-3-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)propanoate;

N-(3-amino-1-(5-chloro-1H-indazol-3-yl)-3-oxopropyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,2-dihydropyrimidine-5-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzamide; and

N-((5-chloro-1H-indazol-3-yl)methyl)-3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide;

and salts thereof.

A specific compound can be further selected from:

N-(4-carbamimidoylbenzyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-(4-(aminomethyl)benzyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-aminopyridin-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((5-chlorobenzo[b]thiophen-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-chlorobenzo[b]thiophen-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-chloro-1H-indol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((5-chloro-1H-indol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((7-chloronaphthalen-2-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-chloronaphthalen-2-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((1-fluoronaphthalen-2-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-chloro-1-fluoronaphthalen-2-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-chloroisoquinolin-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

N-((6-chloroquinolin-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide; and

N-((2-chlorobenzo[b]thiophen-5-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

and salts thereof.

A specific compound can also be selected from:

N-(4-carbamimidoylbenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;

N-(4-(aminomethyl)benzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;

N-((6-aminopyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)- nicotinamide;
N-((6-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((5-chlorobenzo[b]thiophen-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((6-chlorobenzo[b]thiophen-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((6-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((7-chloronaphthalen-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((6-chloronaphthalen-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((1-fluoronaphthalen-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((6-chloro-1-fluoronaphthalen-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)- nicotinamide;
N-((6-chloroisoquinolin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((6-chloroquinolin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide; and
N-((2-chlorobenzo[b]thiophen-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
and salts thereof.

A specific compound can yet further be selected from:
3-(4-((1H-pyrazol-1-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopiperidin-1-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((3-oxomorpholino)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopiperazin-1-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-((2-methylquinolin-6-yl)methyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-((5-((2-oxopyridin-1(2H)-yl)methyl)pyridin-2-yl)methyl)benzamide;
3-((6-amino-5-((2-oxopyridin-1(2H)-yl)methyl)pyridin-2-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)benzamide;
3-((2-amino-6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(2-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(2-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;
3-(2-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(2-hydroxy-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;
3-(2-amino-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;

3-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)benzamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-3-(3-hydroxy-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide;
3-(3-amino-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)benzamide;
and salts thereof.

A specific compound can also be selected from:

5-(4-((1H-pyrazol-1-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopiperidin-1-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((3-oxomorpholino)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopiperazin-1-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-((2-methylquinolin-6-yl)methyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-((5-((2-oxopyridin-1(2H)-yl)methyl)pyridin-2-yl)methyl)nicotinamide;
5-((6-amino-5-((2-oxopyridin-1(2H)-yl)methyl)pyridin-2-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide;
5-((2-amino-6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
5-(2-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2-hydroxy-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
5-(2-amino-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
5-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-hydroxy-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide;
5-(3-amino-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide;
and salts thereof.

A specific compound of the invention can also be selected from:

N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;

N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-cyanoquinolin-3-yl)methyl)isonicotinamide;
3-((4-(((1-aminoisoquinolin-6-yl)methyl)carbamoyl)pyridin-2-yl)methyl)quinoline-6-carboxamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-chloroquinolin-3-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-(hydroxymethyl)quinolin-3-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-(aminomethyl)quinolin-3-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide;
6-((4-(((1-aminoisoquinolin-6-yl)methyl)carbamoyl)pyridin-2-yl)methyl)quinoline-3-carboxamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-(hydroxymethyl)quinolin-6-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methyl-8-sulfamoylquinolin-6-yl)methyl)isonicotinamide;
6-((4-(((1-aminoisoquinolin-6-yl)methyl)carbamoyl)pyridin-2-yl)methyl)-3-methylquinoline-8-carboxylic acid;
N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-methylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-methyl-4-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-cyano-2-methylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-methyl-2-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-cyano-4-methylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-fluoro-2-methylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-chloro-2-methylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-cyano-2-methylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-

yl)methyl)isonicotinamide;

N-((6-amino-2-methyl-5-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-fluoro-8-sulfamoylquinolin-6-yl)methyl)isonicotinamide;

6-((4-(((1-aminoisoquinolin-6-yl)methyl)carbamoyl)pyridin-2-yl)methyl)-3-fluoroquinoline-8-carboxylic acid;

N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-4-methylpyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2-methyl-4-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-4-cyano-2-methylpyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-4-methyl-2-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2-cyano-4-methylpyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-5-fluoro-2-methylpyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-5-chloro-2-methylpyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-5-cyano-2-methylpyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2-methyl-5-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-((3-fluoro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-methylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-fluoro-1H-indazol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((5-chloro-1H-indol-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-6-methyl-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-1H-pyrrolo[3,2-b]pyridin-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((1H-pyrrolo[3,2-b]pyridin-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-methylpyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-methylpyridin-3-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-chloro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-chloro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-chloro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-2-((3-chloro-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide;
N-((6-fluoro-1H-indol-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-fluoro-1H-indazol-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-1H-indol-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;

N-((5-chloro-1H-indol-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-6-methyl-1H-indol-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-1H-pyrrolo[3,2-b]pyridin-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((1H-pyrrolo[3,2-b]pyridin-5-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((1H-benzo[d]imidazol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((3-aminobenzo[d]isoxazol-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((3-amino-1H-indazol-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((2-aminobenzo[d]oxazol-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((2-aminobenzo[d]oxazol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-methylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((3-chloro-1H-indol-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)isoquinolin-6-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methyl-8-sulfamoylisoquinolin-6-yl)methyl)isonicotinamide;
6-((4-(((1-aminoisoquinolin-6-yl)methyl)carbamoyl)pyridin-2-yl)methyl)-3-methylisoquinoline-8-carboxylic acid;
N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)isoquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)isoquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)isoquinolin-6-yl)methyl)isonicotinamide;
N-((5-chloro-1H-indazol-3-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)isoquinolin-6-yl)methyl)isonicotinamide;
N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-((3-methyl-8-(methylsulfonyl)isoquinolin-6-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;
N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methyl-8-sulfamoylquinolin-6-yl)methyl)isonicotinamide;

6-((4-(((1-aminoisoquinolin-6-yl)methyl)carbamoyl)pyridin-2-yl)methyl)-2-methylquinoline-8-carboxylic acid;

N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((2-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-((2-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-((2-methyl-8-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide;

N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((5-(methylsulfonyl)-6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide;

N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((5-(methylsulfonyl)-6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide;

N-((5-chloro-1H-indazol-3-yl)methyl)-2-((5-(methylsulfonyl)-6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide;

N-((6-amino-2-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((6-amino-4-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((6-amino-2-methyl-4-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((6-amino-4-cyano-2-methylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((6-amino-4-methyl-2-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((6-amino-2-cyano-4-methylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((6-amino-5-cyano-2-methylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((6-amino-5-fluoro-2-methylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;

N-((6-amino-5-chloro-2-methylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-

yl)methyl)benzyl)isonicotinamide;
N-((6-amino-2-methyl-5-(trifluoromethyl)pyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-4-(trifluoromethyl)pyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-2-(trifluoromethyl)pyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-4-methyl-2-(trifluoromethyl)pyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-2-cyano-4-methylpyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-5-cyano-2-methylpyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-5-fluoro-2-methylpyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-5-chloro-2-methylpyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-2-methyl-5-(trifluoromethyl)pyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide;
N-((6-amino-4-cyano-2-methylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-methyl-4-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-fluoro-2-methylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-chloro-2-methylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-methyl-5-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-cyano-2-methylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-cyano-4-methylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-methyl-2-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-4-cyano-2-methylpyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-methyl-4-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-fluoro-2-methylpyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-chloro-2-methylpyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-2-methyl-5-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;
N-((6-amino-5-cyano-2-methylpyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;

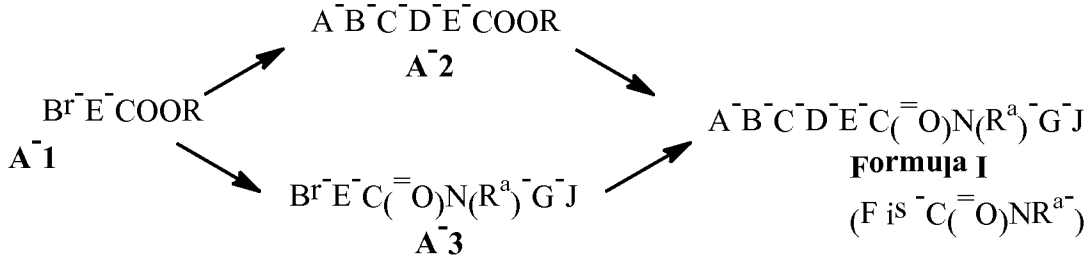
N-((6-amino-2-cyano-4-methylpyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-4-methyl-2-(trifluoromethyl)pyridin-3-yl)methyl)-2-((3-fluoroquinolin-6-yl)methyl)isonicotinamide;

and salts thereof.

Processes for preparing compounds of Formula I and II are provided as further embodiments of the invention and are illustrated by the following Schemes A-D. For example, compounds of Formula I wherein F is $-C(=O)NR^a-$ can be prepared as illustrated in Scheme A.

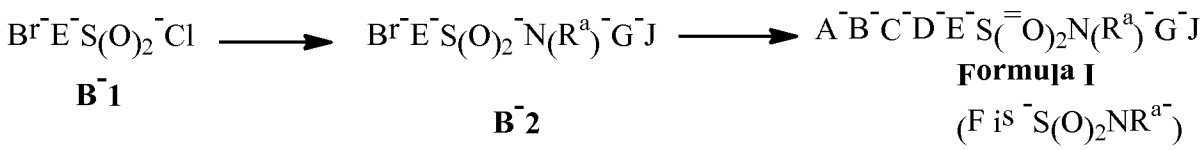
Scheme A



In Scheme A, compounds of Formula I are synthesized by two methods. In one method carboxylic ester **A-1** is converted to **A-2** through a coupling reaction. Examples of coupling reactions include, but are not limited to, Suzuki reaction, Buchwald reaction, Ullmann reaction, SN(AR), and the like. The ester group in **A-2** is then hydrolyzed and coupled with amine to give target compound of Formula I. In another method, carboxylic acid **A-1** is first coupled with a requsite amine to give **A-3**, which is converted to the target compound of Formula I.

Compounds of Formula I wherein F is $-S(=O)_2NR^a-$ can be prepared as shown in Scheme B.

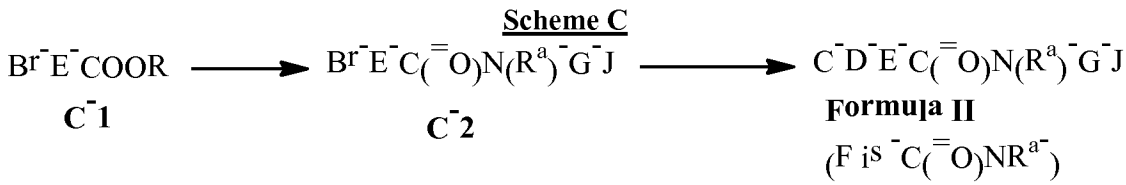
Scheme B



Sulfonyl chloride **B-1** is reacted with a requsite amine to give **B-2**. Various coupling reactions can be run as depicted in Scheme A to give the target compound of Formula I.

Compounds of Formula II where F is $-C(=O)NR^a-$ can be prepared as illustrated in Scheme C.

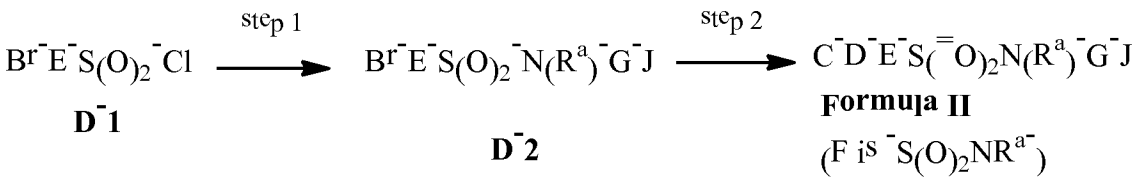
Scheme C



Carboxylic acid **C-1** is coupled with a requsite amine to provide **C-2**. Examples of coupling reactions include, but are not limited to, Suzuki reaction, Buchwald reaction, Ullmann reaction, SN(AR), and the like. Compound **C-2** is then converted to the target compound of Formula II.

Compounds of Formula II wherein F is $-S(=O)_2NR^a-$ can be prepared as shwon in Scheme D.

Scheme D



Sulfonyl chloride **D-1** is reacted with a requsite amine to give **D-2**. Various coupling reactions can be run as depicted in Scheme A to give the target compound of Formula II.

In cases where compounds are sufficiently basic or acidic, a salt of a compound of Formula I or II can be useful as an intermediate for isolating or purifying a compound of Formula I or II. Additionally, administration of a compound of Formula I or II as a pharmaceutically acceptable acid or base salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, trifluoroacetate, citrate, malonate, tartrate, succinate, benzoate, behendate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts. The compounds may also be isolated as solvates.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of Formula I or II can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained. The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit

dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and/or gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various other ingredients enumerated above, as desired, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads,

used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of dermatological compositions for delivering active agents to the skin are known to the art; for example, see U.S. Patent Nos. 4,992,478 (Geria), 4,820,508 (Wortzman), 4,608,392 (Jacquet et al.), and 4,559,157 (Smith et al.). Such dermatological compositions can be used in combinations with the compounds described herein where an ingredient of such compositions can optionally be replaced by a compound described herein, or a compound described herein can be added to the composition.

Useful dosages of the compounds of Formula I or II can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949 (Borch et al.). The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg, e.g., from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

The compound is conveniently formulated in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form. In one embodiment, the invention provides a composition comprising a compound of the invention formulated in such a unit dosage form.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

A disease or condition in an animal wherein inhibition of plasma kallikrein is indicated includes the diseases and conditions recited above in the Background section above. A specific condition where inhibition of plasma kallikrein is indicated is genetic angioedema or 'hereditary angioedema' ("HAE").

The ability of a compound of the invention to inhibit plasma kallikrein may be determined using pharmacological models which are well known to the art, or using Test A described below.

Test A.

A 10 mM solution of a test compound ('Compound X') was made in DMSO. This solution was serially diluted 1 in 5 in DMSO to yield 2000, 400, 80, 16, 3.2, 0.64, 0.128, 0.0256 and 0.00512 μM solutions, hereby referred to as "100X Compound X DMSO stocks". A control tube containing only DMSO was

included. 16 µL of each 100X DMSO stock dilution was combined with 384 µL of assay buffer (50 mM Tris-HCl pH 7.5, 150 mM NaCl, 0.01% Triton X-100) to yield a "4X Compound X buffer stock".

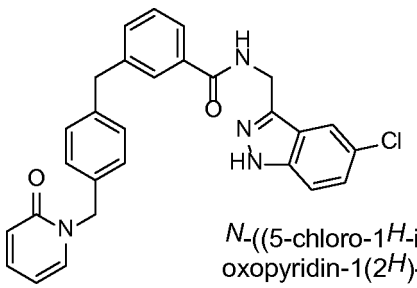
Separately, a 40 nM solution of human Plasma Kallikrein (Abcam) and a 93.6 µM solution Pro-Phe-Arg-AMC (Bachem) were made using assay buffer. These solutions are hereby known as 4X hPK and 2X PFR-AMC, respectively.

60 µL of each 4X Compound X Buffer stock was combined with 60µL of 4X hPK to yield 120 µL of "2X Compound X Buffer stock/2X hPK". 50 µL was removed from this mixture and placed into duplicate wells on a Microfluor 1Black U-bottom microtiter plate (Thermo Scientific). This plate was incubated for 5 minutes at 37 °C. To each well, 50 µL of pre-warmed 2X PFR-AMC was added to start the enzymatic reaction. Cleavage of PFR-AMC was monitored in a Biotek Synergy H4 reader set at 37 °C. Readings were taken every 43 seconds for 1 hour. The highest mean velocity over 20 reads (~15 minutes) was used to calculate the IC_{50}. The IC_{50} was calculated using the Gen5 (Biotek Instruments).

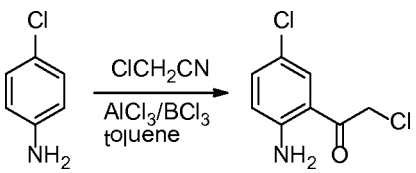
The invention will now be illustrated by the following non-limiting Examples.

EXAMPLES

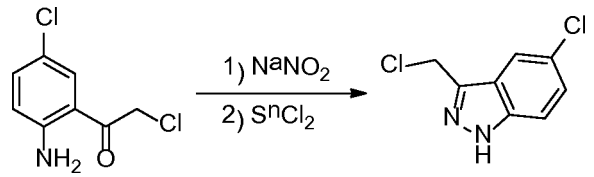
Example 1: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide



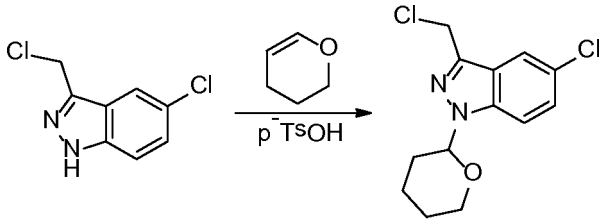
N-((5-chloro-1*H*-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)benzamide



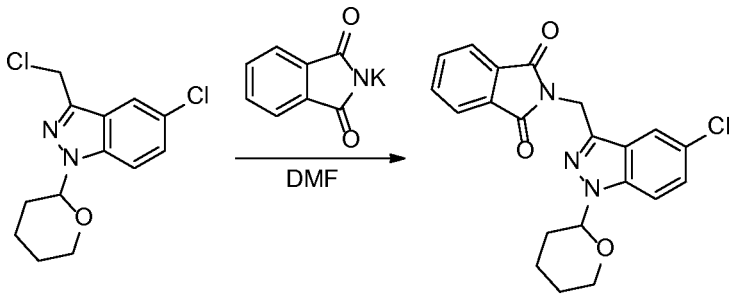
To a stirred solution of boron trichloride in toluene (200 mL, 1 M, 0.2 mol, 1.16 eq), a solution of 4-chloroaniline (22.0 g, 0.172 mol, 1.0 eq) in dry toluene (200 mL) was added dropwise under nitrogen at a temperature ranging from 5 °C to 10 °C. To the resulting mixture, chloroacetonitrile (15 mL, 0.237 mol, 1.38 eq) and aluminum trichloride (29.0 g, 0.217 mol, 1.26 eq) were added successively. The mixture was refluxed for 18 h. After cooling, ice-cold hydrochloric acid (2 N, 500 mL) was added and a yellow precipitate was formed. The mixture was warmed at 80 °C with stirring, until the precipitate was dissolved. The cooled solution was extracted with dichloromethane (250 mL X 3). The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The resulting residue was purified on silica gel column (PE/EtOAc = 50/1 ~ PE/EA/DCM = 1/8/1, v/v/v) to afford 1-(2-amino-5-chlorophenyl)-2-chloroethanone as a yellow brown solid (18.3 g, 52 %).



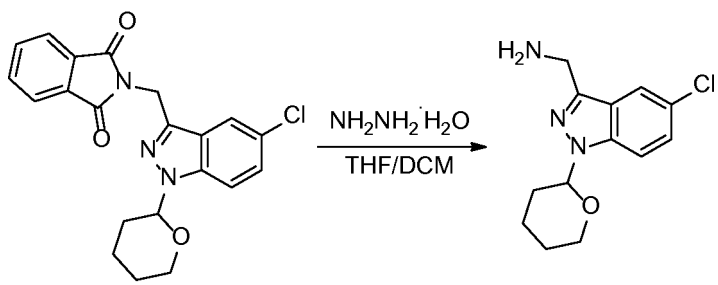
To a stirred suspension of 1-(2-amino-5-chlorophenyl)-2-chloroethanone (16 g, 78 mmol, 1.0 eq) in conc. hydrochloric acid (120 mL) was added a solution of sodium nitrite (5.9 g, 86 mmol, 1.1 eq) in water (30 mL) at 0 °C. After 1 h, a solution of $SnCl_2 \cdot 2H_2O$ (42.3 g, 187 mmol, 2.4 eq) in conc. hydrochloric acid (60 mL) was added to the reaction mixture and stirred for 1 h. Ice-water was added to the reaction mixture. The precipitate was collected by filtration, washed with water and dried to afford crude 5-chloro-3-(chloromethyl)-1H-indazole, which was used in the next step without further purification (13.5 g, 86%).



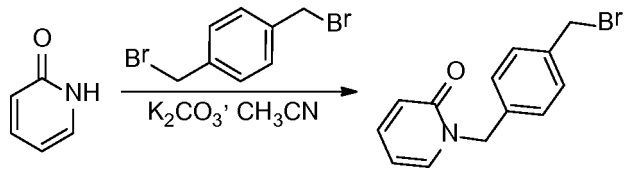
A solution of 5-chloro-3-(chloromethyl)-1H-indazole (13.5 g, 67 mmol, 1.0 eq), 3,4-dihydro-2H-pyran (11.3 g, 134 mmol, 2.0 eq) and p-toluenesulfonic acid monohydrate (1.27 g, 6.7 mmol, 0.1 eq) in THF (300 mL) was stirred at 70 °C for 12 h. After cooling to rt (~22 °C), the reaction mixture was mixed with water (300 mL) and extracted with EA (200 mL ×2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford 5-chloro-3-(chloromethyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole as a yellow solid (16 g, 84%).



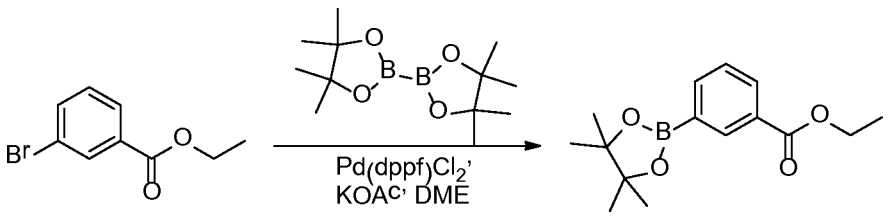
To a solution of 5-chloro-3-(chloromethyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (18 g, 63 mmol, 1 eq) in anhydrous DMF (200 mL) under N_2, potassium phthalimide (17.5 g, 94 mmol, 1.5 eq) was added and the resulting mixture was heated at 90 °C for 2 h. The mixture was poured into water and extracted with DCM (200 mL X 2). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was washed with EtOH to afford 2-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)isoindoline-1,3-dione as a white solid (15 g, 60%).



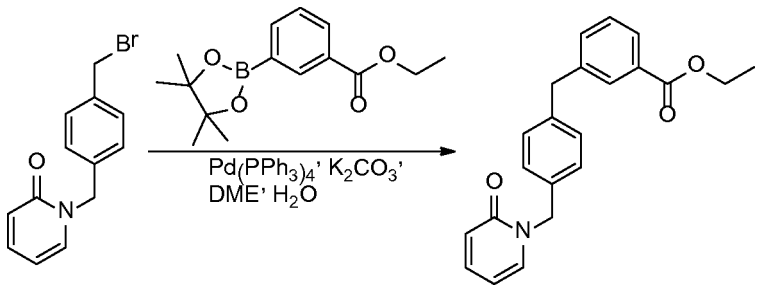
To a solution of 2-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)isoindoline-1,3-dione (15 g, 37.9 mmol, 1.0 eq) in THF (300 mL) and DCM (60 mL) was added hydrazine hydrate (9.5 g, 189 mmol, 5 eq). The white suspension was stirred at 48 °C for 12 h and phthalyl hydrazide was removed by filtration. The filtrate was concentrated in vacuo and the crude material was dissolved in DCM and washed with 1 N NaOH solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine as a yellow solid (9.9 g, 99%).



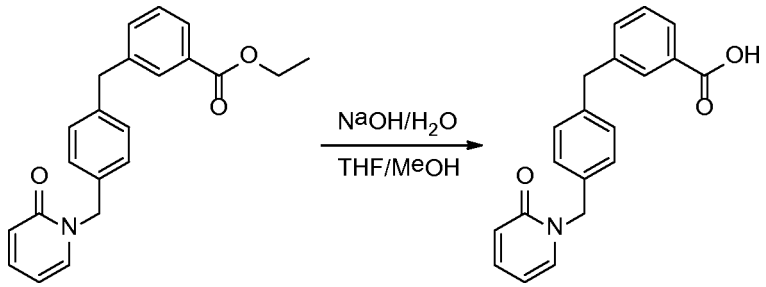
The mixture of pyridin-2(1H)-one (6.0 g, 63.1 mmol, 1.0 eq), 1,4-bis(bromomethyl)benzene (50.0 g, 189.4 mmol, 3.0 eq) and potassium carbonate (8.7 g, 63.1 mmol, 1.0 eq) in CH_3CN (350 mL) was stirred at 80 °C overnight. After cooled to rt, to the mixture was added water (300 mL). The precipitate was filtered and rinsed with EtOH to recover 1,4-bis(bromomethyl)benzene; the filtrate was extracted with DCM (100 mL X 2), the extracts were washed with water, brine and dried over anhydrous Na_2SO_4, filtered and concentrated to afford 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one as a white solid (8.5 g, 48%).



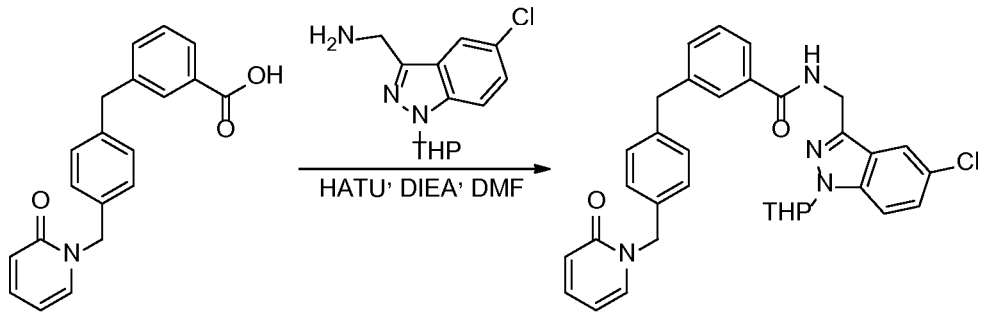
A mixture of ethyl 3-bromobenzoate (2.29 g, 10 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.05 g, 12 mmol, 1.2 eq), Pd(dppf)Cl_2 (732 mg, 1 mmol, 0.1 eq), KOAc (2.94 g, 30 mmol, 3 eq) in DME (50 mL) under N_2 was stirred at 90 °C overnight and concentrated. The resulting residue was purified via flash chromatography (PE/EA = 50/1, v/v) to afford ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate as a yellow oil (2.64 g, 95%).



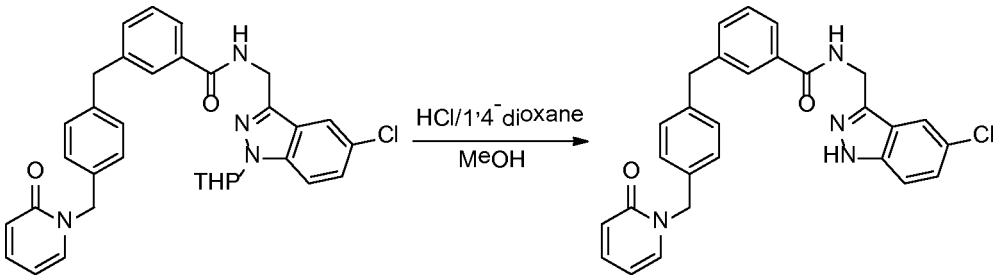
A mixture of ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2.64 g, 9.57 mmol, 1.16 eq), 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (2.30 g, 8.27 mmol, 1 eq), Pd(PPh_3)$_4$ (1.16 g, 1 mmol, 0.12 eq), K_2CO_3 (4.14 g, 30 mmol, 3.6 eq) in DME/H_2O (60 mL/15 mL) under N_2 was stirred at 90 °C overnight and concentrated. The resulting residue was extracted with EA (50 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via flash chromatography (PE/EA=9/1-1/1, v/v) to afford ethyl 3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzoate as a colorless oil (3.10 g crude, quant.).



To a solution of ethyl 3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzoate (3.10 g, crude, 1.0 eq) in MeOH (15 mL) and THF (10 mL) was added 2 N NaOH aqueous solution (20 mL). The mixture was stirred at rt overnight. The mixture was concentrated. To the resulting residue was added conc. HCl to adjust to pH 2. The precipitate was collected and dried to afford 3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzoic acid as a white solid (2.64 g, quant.).

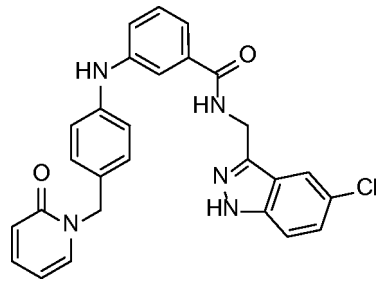


A mixture of 3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzoic acid (320 mg, 1 mmol, 1 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (320 mg crude, 1.2 mmol, 1.2 eq), HATU (570 mg, 1.5 mmol, 1.5 eq) and DIEA (1 mL) in DMF (5 mL) was stirred at 60 °C overnight. The mixture was poured into water (20 mL). The precipitate was collected and purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide as a yellow solid (288 mg, 50%).

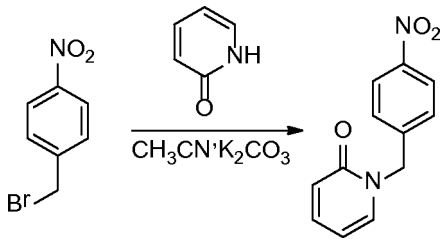


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide (100 mg, 0.176 mmol, 1 eq) in MeOH (3 mL) and HCl/dioxane (5 N, 2 mL) was stirred at rt overnight, then concentrated. The resulting residue was suspended in $NaHCO_3$ solution. The precipitate was collected and purified via prep-TLC (DCM/MeOH = 10/1, v/v) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide as a yellow solid (60 mg, 70%). LRMS ($M+H^+$) m/z calculated 483.2, found 483.2. ^1H NMR (DMSO-*d6*, 300 MHz) δ 13.06 (s, 1 H), 9.09 (t, 1 H), 7.90 (d, 1 H), 7.75-7.67 (m, 3 H), 7.52 (d, 1 H), 7.42-7.31 (m, 4 H), 7.20 (s, 4 H), 6.38 (d, 1 H) , 6.21 (t-d, 1 H), 5.03 (s, 2 H), 4.76 (d, 2 H), 3.94 (d, 2 H).

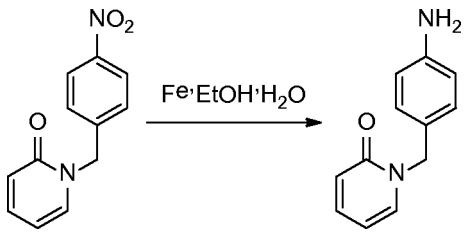
Example 2: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzamide



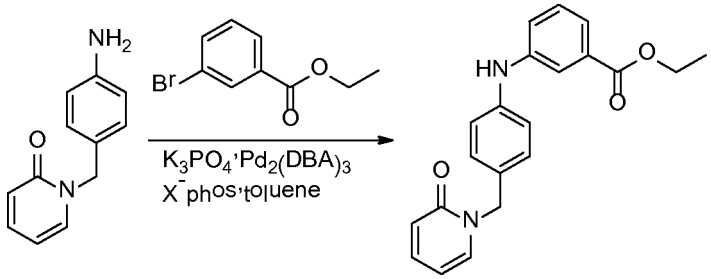
N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzamide



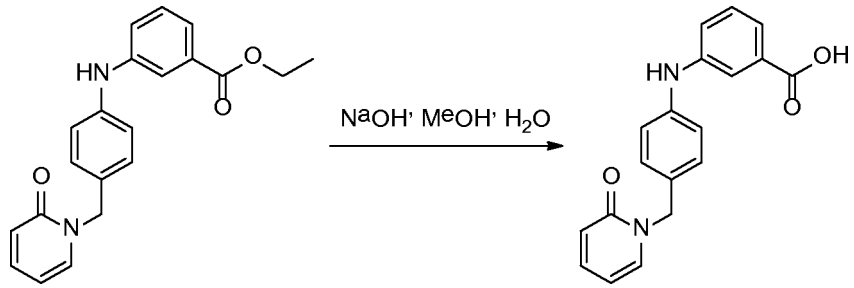
To a solution of 1-(bromomethyl)-4-nitrobenzene (2.3 g, 10.5 mmol, 1.0 eq) in CH_3CN (20 mL) were added K_2CO_3 (2.9 g, 21 mmol, 2.0 eq) and pyridin-2(1H)-one (1.0 g, 10.5 mmol, 1.0 eq). The mixture was heated at 80 °C overnight. The mixture was concentrated under reduced pressure, mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via silica gel column (PE/EA = 5/1 to DCM/MeOH = 200/1, v/v) to afford 1-(4-nitrobenzyl)pyridin-2(1H)-one as a yellow solid (1.9 g, 79 %).



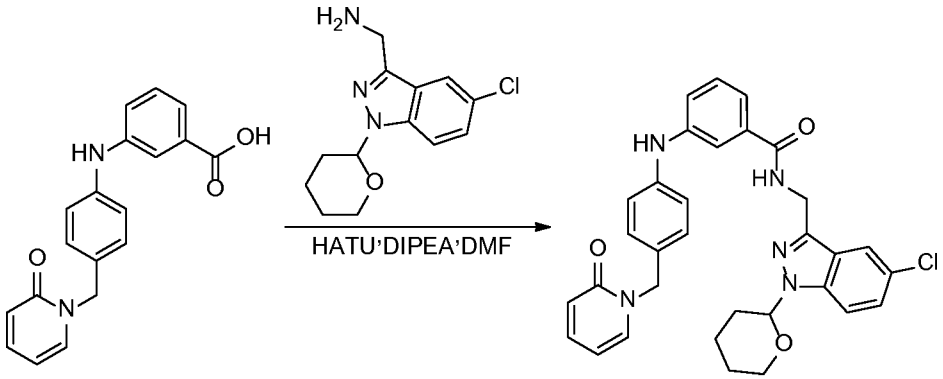
To a solution of 1-(4-nitrobenzyl)pyridin-2(1H)-one (1.9 g, 8.3 mmol, 1.0 eq) in EtOH (20 mL) and H_2O (20 mL) was added Fe (1.9 g, 33 mmol, 4.0 eq). The mixture was heated to 80 °C, con.HCl (0.1 mL, 0.8 mmol, 0.1 eq) was then added dropwise. The resulting mixture was heated at 80 °C overnight. The mixture was adjusted to pH 10 with 15% KOH in EtOH, and filtered. The filter cake was washed with EtOH (20 mL X 2). The combined filtrate was concentrated to remove EtOH, the aqueous residue was extracted with EA (50 mL X 6). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via silica gel column (DCM/MeOH= 200/1 to 100/1, v/v) to afford 1-(4-aminobenzyl)pyridin-2(1H)-one as a yellow solid (1.3 g, 79%).



To a solution of 1-(4-aminobenzyl)pyridin-2(1H)-one (500 mg, 2.5 mmol, 1.0 eq.) in toluene (15 mL) were added ethyl 3-bromobenzoate (630 mg, 2.7 mmol, 1.1 eq), K_3PO_4 (1.06 g, 5 mmol, 2.0 eq), $Pd_2(DBA)_3$ (36 mg, 0.0375 mmol, 0.015 eq) and X-phos (58 mg, 0.1 mmol, 0.04 eq) at rt. The mixture was heated at 120 °C overnight under N_2. After cooled to 25 °C, the mixture was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via silica gel column (DCM/MeOH = 200/1, v/v) to afford ethyl 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzoate as a white solid (460 mg, 53%).

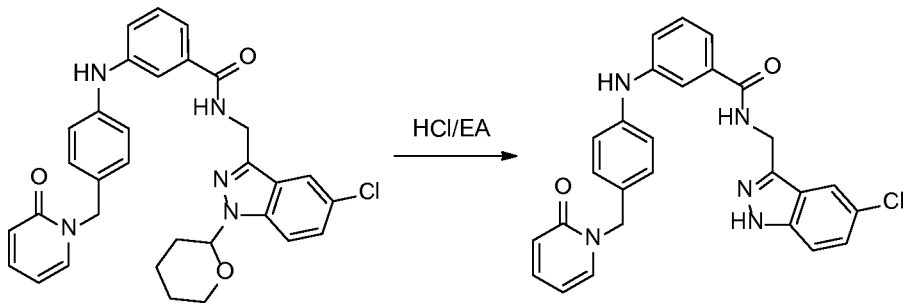


To a solution of ethyl 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzoate (460 mg, 1.3 mmol, 1.0 eq) in MeOH (4 mL) and H_2O (4 mL) was added NaOH (160 mg, 4 mmol, 3.0 eq). The mixture was heated at 60 °C for 30 min. The mixture was concentrated to remove MeOH, then diluted with ice-water (10 mL) and acidified with 1 N HCl to pH 2~3. The mixture was concentrated under reduced pressure. The resulting residue was re-dissolved in MeOH (20 mL) and filtered. The filtrate was concentrated to afford 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzoic acid as a white solid (450 mg crude, quant.).



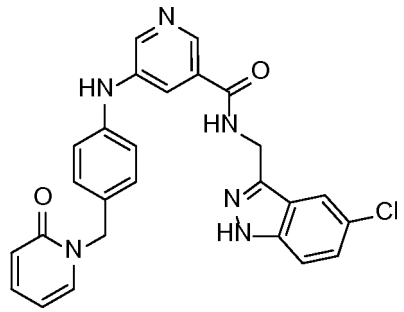
To a solution of 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzoic acid (200 mg, 0.63 mmol, 1.0 eq) in DMF (5 mL) were added DIPEA (242 mg, 1.88 mmol, 3.0 eq) and HATU (285 mg, 0.75 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (166 mg, 0.63 mmol, 1.0 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated.

The resulting residue was purified via prep-TLC (DCM/MeOH = 20/1, v/v) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzamide as a white solid (100 mg, 28%).

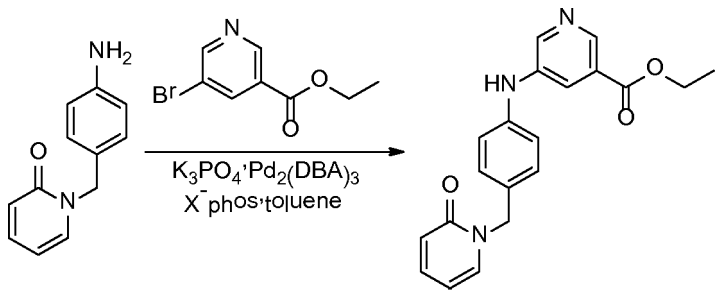


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzamide (100 mg, 0.18 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/EA (2 mL, 4 mmol) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure. The resulting residue was mixed with water (10 mL), neutralized with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via prep-TLC (DCM/MeOH = 20/1, v/v) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzamide as a white solid (40 mg, 47%). LRMS ($M+H^+$) m/z caculated 484.2, found 484.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.04 (brs, 1 H), 9.00-9.05 (m, 1 H), 8.36 (s, 1 H), 7.90 (d, 1 H), 7.70-7.80 (m, 1 H), 7.50-7.60 (m, 2 H), 7.10-7.45 (m, 7 H), 7.00-7.05 (m, 2 H), 6.39 (d, 1 H), 6.22 (t, 1 H), 4.99 (s, 2 H), 4.76 (d, 2 H).

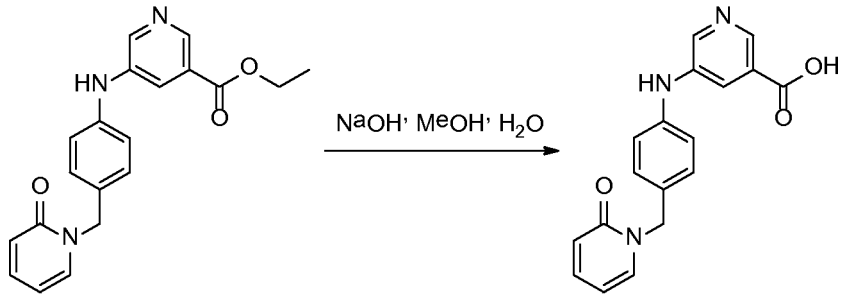
Example 3: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinamide



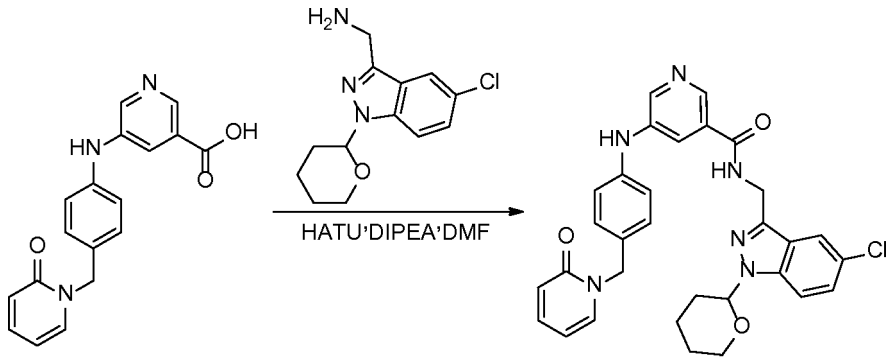
N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2*H*)-yl)methyl)phenyl)amino)nicotinamide



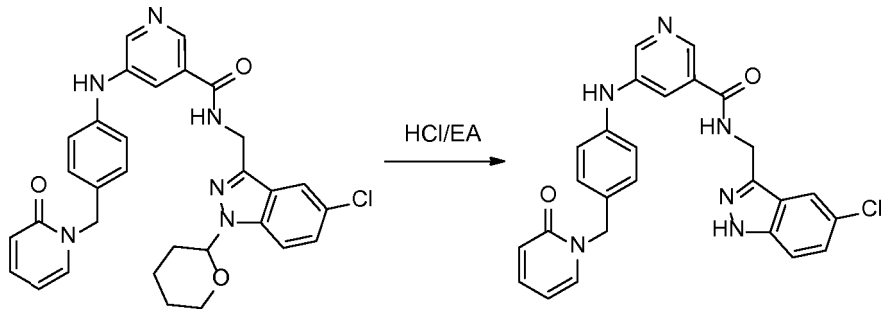
To a solution of 1-(4-aminobenzyl)pyridin-2(1H)-one (500 mg, 2.5 mmol, 1.0 eq) in toluene (15 mL) were added ethyl 5-bromonicotinate (633 mg, 2.7 mmol, 1.1 eq), K_3PO_4 (1.06 g, 5 mmol, 2.0 eq), $Pd_2(DBA)_3$ (36 mg, 0.0375 mmol, 0.015 eq) and X-phos (58 mg, 0.1 mmol, 0.04 eq) at rt. The mixture was heated at 120 °C overnight under N_2. After cooled to 25 °C, the mixture was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via silica gel column (DCM/MeOH = 200/1, v/v) to afford ethyl 5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinate as a yellow solid (350 mg, 40%).



To a solution of ethyl 5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinate (350 mg, 1 mmol, 1.0 eq) in MeOH (5 mL) and H_2O (5 mL) was added NaOH (120 mg, 3 mmol, 3.0 eq). The mixture was heated at 60 °C for 30 min. The mixture was concentrated to remove MeOH, then diluted with ice-water (10 mL) and acidified with 1 N HCl to pH 2~3. The mixture was concentrated under reduced pressure. The resulting residue was re-dissolved in MeOH (20 mL) and filtered. The filtrate was concentrated to afford 5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinic acid as a yellow solid (400 mg crude, quant.).

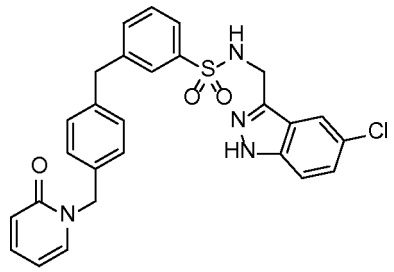


To a solution of 5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinic acid (400 mg crude, 1 mmol, 1.0 eq) in DMF (5 mL) were added DIPEA (387 mg, 3 mmol, 3.0 eq) and HATU (456 mg, 1.2 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (266 mg, 1 mmol, 1.0 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinamide as a white solid (300 mg, 53%).

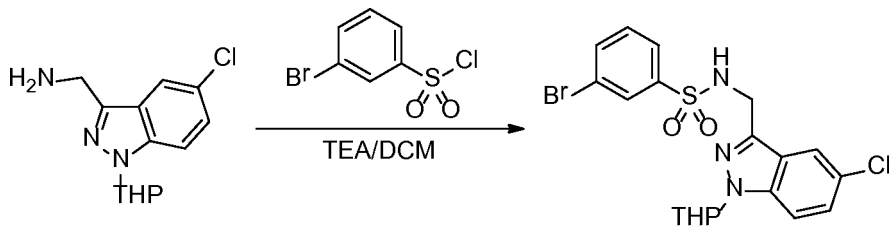


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinamide (300 mg, 0.53 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/EA (2 mL, 4 mmol) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure. The resulting residue was mixed with water (10 mL), neutralized with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinamide as a white solid (30 mg, 12%). LRMS ($M+H^+$) m/z caculated 485.2, found 485.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.20-9.27 (m, 1 H), 8.58 (s, 1 H), 8.45 (s, 1 H), 8.39 (d, 1 H), 7.90 (s, 1 H), 7.80-7.84 (m, 1 H), 7.78 (d, 1 H), 7.53 (d, 1 H), 7.40 (t, 1 H), 7.33 (d, 1 H), 7.25 (d, 2 H), 7.08 (d, 2 H), 6.40 (d 1 H), 6.22 (t, 1 H), 5.01 (s, 2 H), 4.77 (d, 2 H).

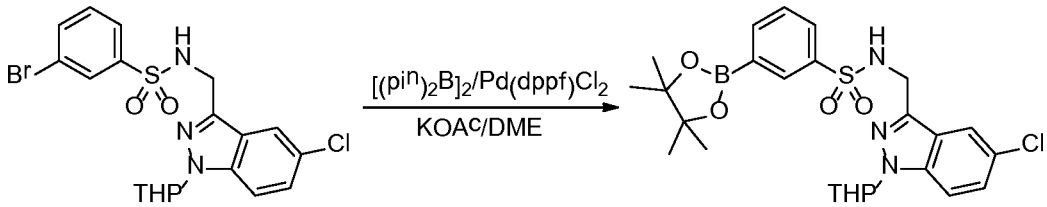
Example 4: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzenesulfonamide



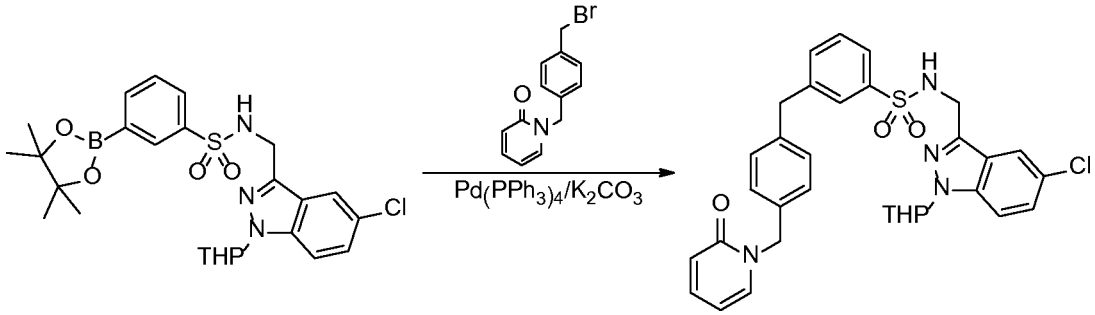
N-((5-chloro-1*H*-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)benzenesulfonamide



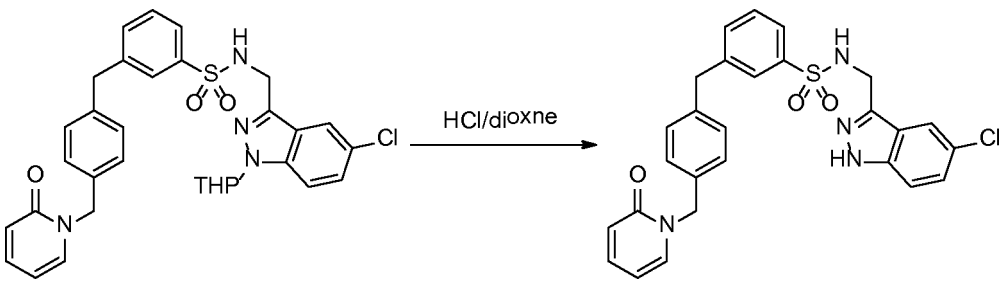
The mixture of (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (2.8 g, 10.7 mmol, 1.0 eq), 3-bromobenzene-1-sulfonyl chloride (3.0 g, 11.7 mmol, 1.1 eq) and triethylamine (3.24 g, 32.1 mmol, 3.0 eq) in DCM (50 mL) was stirred at rt overnight. Then the mixture was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified on silica gel column (PE/EA = 2:1, v/v) to afford 3-bromo-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)benzenesulfonamide as a yellow oil (4.8 g, 84%).



The minture of 3-bromo-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)benzenesulfonamide (500 mg, 1.03 mmol, 1.1 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (314 mg, 1.24 mmol, 1.2 eq), $Pd(dppf)Cl_2$ (73 mg, 0.1 mmol, 0.1 eq) and KOAc (304 mg, 3.1 mmol, 3.0 eq) in 1,2-dimethoxyethane (20 mL) was stirred at 90 °C under N_2 overnight. Then the mixture was concentrated. The resulting residue was diluted with EtOAc (50 mL), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified on silica gel column (PE/EtOAc = 2/1, v/v) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide as a yellow oil (500 mg, 97%).



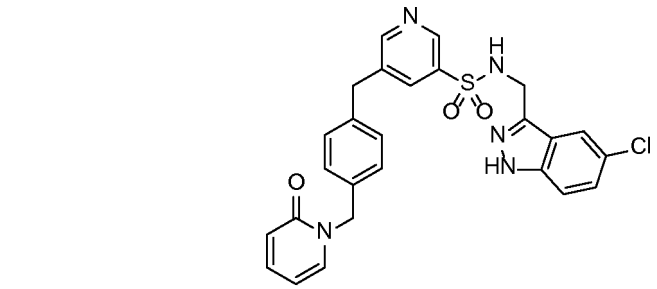
The minture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (800 mg, 1.5 mmol, 1.2 eq), 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (350 mg, 1.26 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (95 mg, 0.13 mmol, 0.1 eq) and K_3PO_4 (801 mg, 3.78 mmol, 3.0 eq) in DMF/H_2O (20 mL/2 mL) was stirred at 110 °C under N_2 overnight. Then the mixture was concentrated. The resulting residue was diluted with EtOAc (50 mL), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column (PE/EtOAc = 1/1, v/v) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzenesulfonamide as a yellow solid (360 mg, 47%).



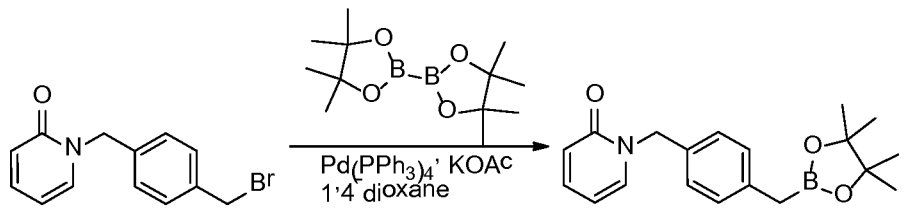
N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzenesulfonamide (360 mg, 0.6 mmol, 1.0 eq) was dissolved in HCl/1,4-dioxane (2 M, 20 mL) and stirred at rt for 2 h. Then the mixture was concentrated in vacuo, and the resulting residue was purified by pre-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-

yl)methyl)benzyl)benzenesulfonamide as yellow solid (27.8 mg, 9%). LCMS ($M+H^+$) m/z calculated 519.1, found 518.8. ^1H NMR (CD_3OD, 300 MHz) δ 7.68-7.57 (m, 3H), 7.54-7.48 (m, 1H), 7.39 (d, 1H), 7.34-7.22 (m, 5H), 7.14 (d, 1H), 6.57 (d, 1H), 6.37 (dt, 1H), 5.16 (s, 2H), 4.40 (s, 2H), 3.91 (d, 1H).

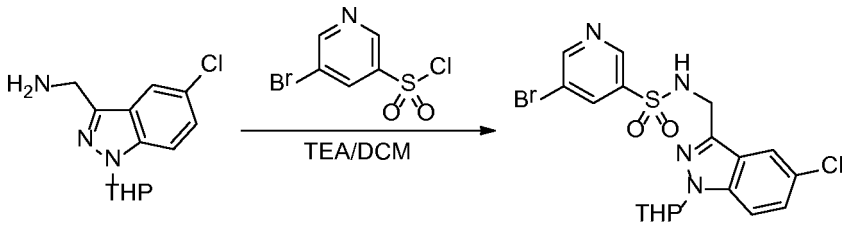
Example 5: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-3-sulfonamide



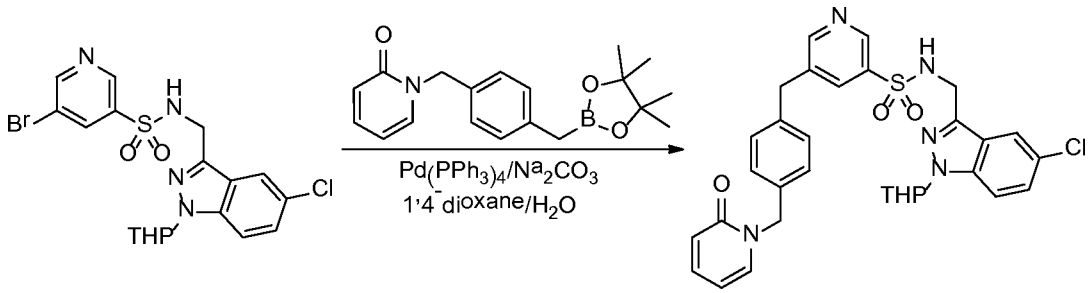
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-3-sulfonamide



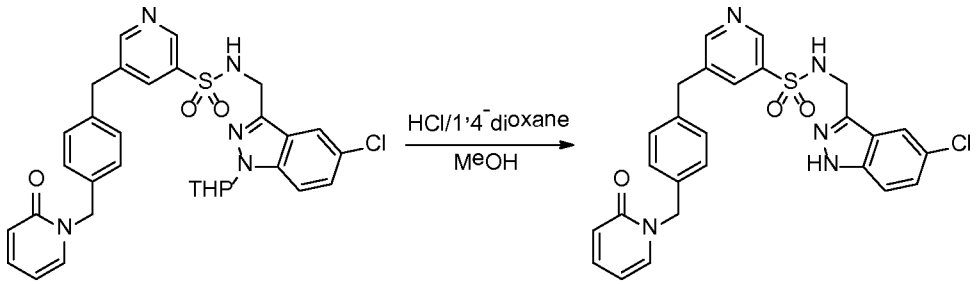
Potassium acetate (1.9 g, 19.4 mmol, 3.0 eq), bis(pinacolato)diboron (1.98 g, 7.76 mmol, 1.2 eq) and tetrakis(triphenylphosphine)palladium (374 mg, 0.323 mmol, 0.05 eq) were added to a solution of 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (1.8 g, 6.47 mmol, 1.0 eq) in dioxane (120 mL) and the mixture was heated at 80 °C for 3 h and allowed to cool. The mixture was concentrated, and the resulting residue was purified on silica gel column (PE/EA = 3/1 then DCM/MeOH = 15/1, v/v) to afford 1-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzyl)pyridin-2(1H)-one as a white solid (1.0 g, 47%).



A mixture of 5-bromopyridine-3-sulfonyl chloride (257 mg, 1 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (310 mg, 12 mmol, 1.2 eq) and Et_3N (1 mL) in DCM (10 mL) was stirred at rt overnight and then concentrated. The resulting residue was purified via flash chromatography (PE/EA/DCM=1/2/1, v/v/v) to afford 5-bromo-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)pyridine-3-sulfonamide as a white solid (451 mg, 92%).

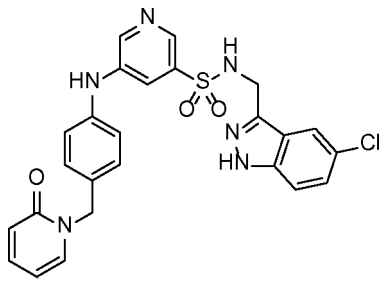


A mixture of 5-bromo-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)pyridine-3-sulfonamide (99 mg, 0.20 mmol, 1.0 eq), 1-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzyl)pyridin-2(1H)-one (85 mg, 0.26 mmol, 1.3 eq), $Pd(PPh_3)_4$ (27 mg, 0.023 mmol, 0.115 eq), Na_2CO_3 (106 mg, 1 mmol, 5 eq) in 1,4-dioxane/H_2O (5 mL/0.5 mL) under N_2 was stirred at 90 °C overnight and then concentrated. The resulting residue was purified via prep-TLC (DCM/MeOH = 12/1, v/v) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-3-sulfonamide as a white solid (92 mg, 74%).

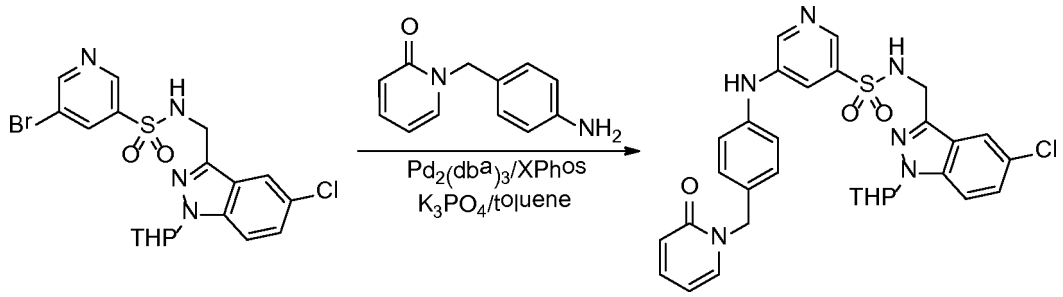


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-3-sulfonamide (92 mg, 0.15 mmol, 1 eq) in MeOH (2 mL) and HCl/dioxane (5 N, 2 mL) was stirred at rt overnight, then concentrated. The resulting residue was suspended in $NaHCO_3$ solution. The precipitate was collected and purified via prep-TLC (DCM/MeOH = 12/1, v/v) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-3-sulfonamide as a white powder (50 mg, 63%). LRMS ($M+H^+$) m/z calculated 520.1, found 520.1. ^1H NMR (CD3OD-*d6*, 300 MHz) δ 8.56 (d, 1 H), 8.34 (d, 1 H), 7.70-7.65 (m, 3 H), 7.56-7.50 (m, 1 H), 7.38 (d, 1 H), 7.31-7.25 (m, 3 H), 7.14 (s, 1 H), 7.12 (s, 1 H), 6.57 (d, 1 H) , 6.39 (t, 1 H), 5.18 (s, 2 H), 4.51 (s, 2 H), 3.88 (s, 2 H).

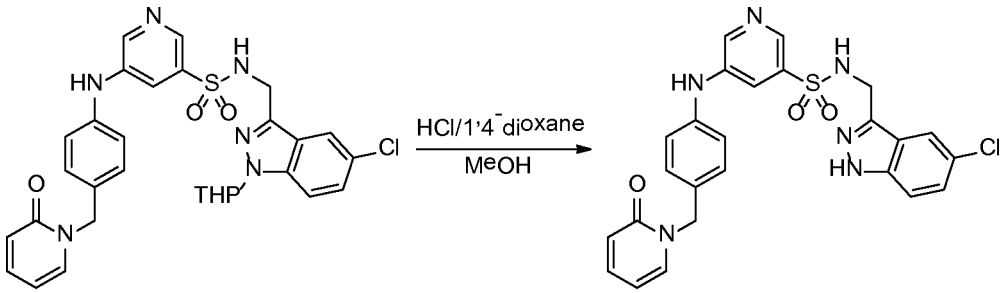
Example 6: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)pyridine-3-sulfonamide



N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2*H*)-yl)methyl)phenyl)amino)pyridine-3-sulfonamide

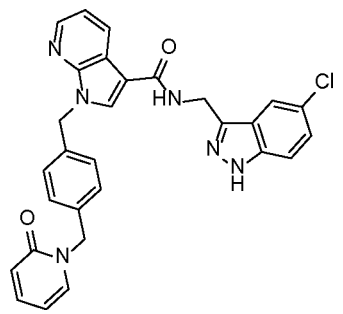


A mixture of 5-bromo-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)pyridine-3-sulfonamide (243 mg, 0.5 mmol, 1.0 eq), 1-(4-aminobenzyl)pyridin-2(1H)-one (121 mg, 0.6 mmol, 1.2 eq), $Pd_2(dba)_3$ (50 mg, 0.05 mmol, 0.1 eq), K_3PO_4 (318 mg, 1.5 mmol, 3 eq) in toluene (5 mL) under N_2 was refluxed overnight and then filtered. The filtrate was concentrated. The resulting residue was purified via prep-TLC (DCM/MeOH = 12/1, v/v) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)pyridine-3-sulfonamide as a light yellow solid (72 mg, 23%).

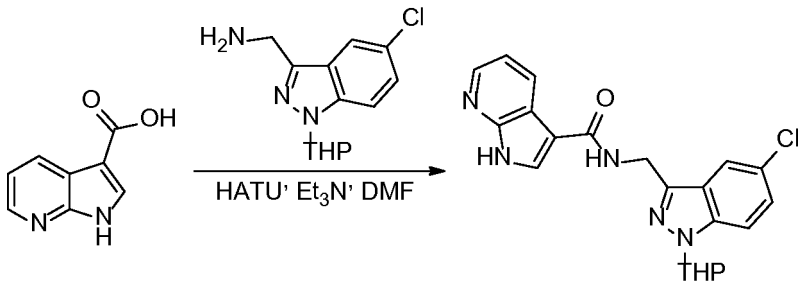


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)pyridine-3-sulfonamide (72 mg, 0.12 mmol, 1 eq) in MeOH (2 mL) and HCl/dioxane (5 N, 1 mL) was stirred at rt overnight, then concentrated. The resulting residue was triturated with Et_2O (5 mL) and DCM (10 mL) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)pyridine-3-sulfonamide HCl salt as a yellow powder (60 mg, 90%). LRMS ($M+H^+$) m/z calculated 521.1, found 520.8. ^1H NMR (CD_3OD-*d6*, 300 MHz) δ 8.13 (d, 2 H), 7.93 (dd, 1 H), 7.84-7.83 (m, 1 H), 7.74-7.69 (m, 2 H), 7.45-7.41 (m, 3 H), 7.33-7.30 (m, 1 H), 7.17-7.14 (m, 2 H), 6.75 (d, 1 H) , 6.64 (t-d, 1 H), 5.30 (s, 2 H), 4.64 (s, 2 H).

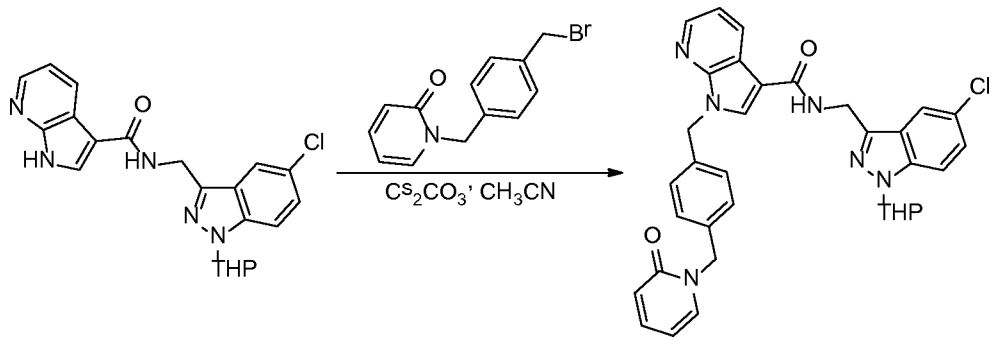
Example 7: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide



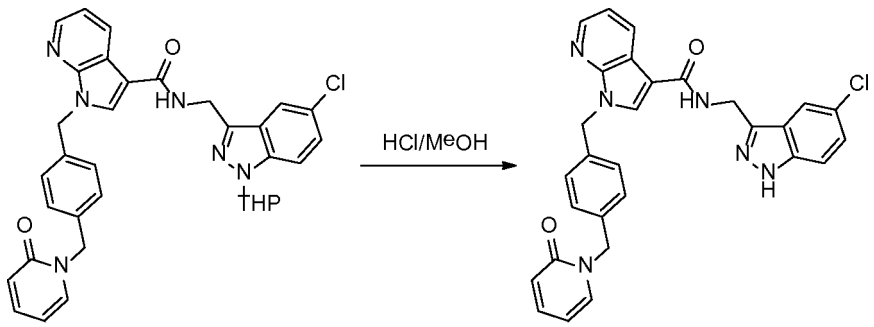
N-((5-chloro-1*H*-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide



To a solution of 1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid (162 mg, 1 mmol, 1.0 eq) in DMF (8 mL) were added HATU (570 mg, 1.5 mmol, 1.5 eq) and Et_3N (0.3 mL, 2.0 mmol, 2.0 eq). The mixture was stirred at rt for 15 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (265 mg, 1.0 mmol, 1.0 eq) was then added. The resulting mixture was stirred at rt overnight, then mixed with water and extracted with DCM (50 mL X 2). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified via silica gel column (DCM/MeOH = 10/1, v/v) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (380 mg, 92%).



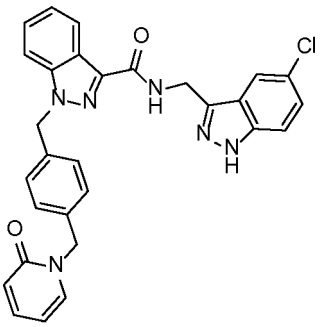
A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (380 mg, 0.93 mmol, 1.0 eq), 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (258 mg, 0.93 mmol, 1.0 eq) and Cs_2CO_3 (1.05 g, 1.8 mmol, 2.0 eq) in CH_3CN (20 mL) was stirred at 80 °C overnight. The reaction mixture was poured into water and extracted with DCM (50 mL X 2). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified via flash chromatography (reverse, 30-95% CH_3CN in water) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide as a white solid (130 mg, 21%).



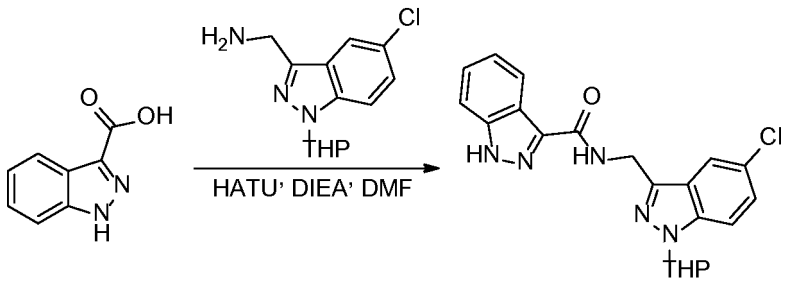
To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (130 mg, 0.21 mmol, 1.0 eq) in MeOH (2

mL) was added concentrated HCl (0.5 mL, 6 mmol). The mixture was stirred at rt for 2 h, and then concentrated in vacuo. The resulting residue was neutralized with saturated aqueous sodium bicarbonate solution, the precipitate was collected by filtration, further purified by preparative TLC (5% MeOH in DCM) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide as a white solid. LRMS ($M+H^+$) m/z calculated 523.0, found 522.8. ^1H NMR (DMSO-*d6*, 300 MHz) δ 13.03 (s, 1 H), 8.69-8.65 (t, 1 H), 8.52-8.50 (d, 1 H), 8.33-8.31 (d, 1 H), 8.24 (s, 1H), 7.92 (s, 1 H), 7.73-7.70 (d, 1H), 7.537.50 (d, 1H), 7.31-7.21 (m, 7H), 6.38-6.35 (d, 1H), 6.20-6.18 (t, 1H), 5.46 (s, 2H), 5.02 (s, 2H), 4.77-4.75 (d, 2H).

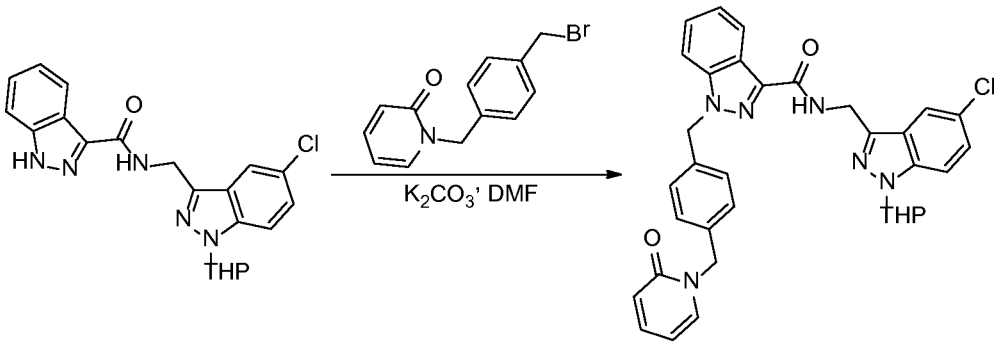
Example 8: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indazole-3-carboxamide



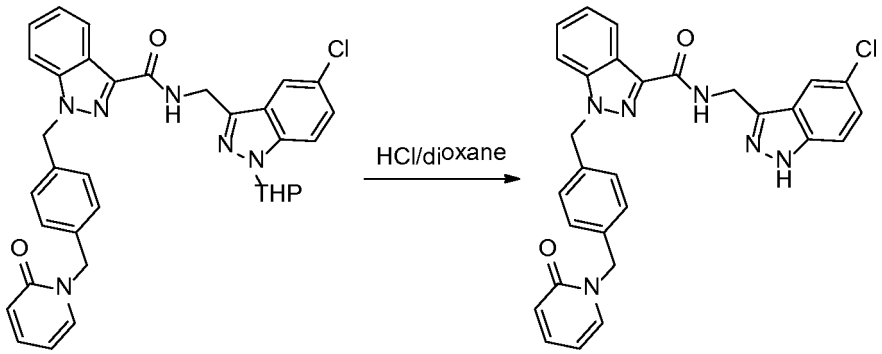
N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indazole-3-carboxamide



To a solution of 1H-indazole-3-carboxylic acid (324 mg, 2.0 mmol, 1.0 eq) in DMF (10 mL) were added HATU (1.14 g, 3.0 mmol, 1.5 eq) and DIEA (768 mg, 6.0 mmol, 3.0 eq). The mixture was stirred at rt for 30 min. Then (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (584 mg, 2.2 mmol, 1.1 eq) was added. The resulting mixture was stirred at 80 °C overnight. The mixture was poured into water and extracted with EtOAc (50 mL X 2). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified on silica gel column (PE/EtOAc = 5/1, v/v) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1H-indazole-3-carboxamide as a yellow solid (410 mg, 50%).

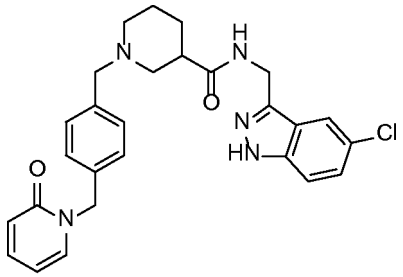


A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1H-indazole-3-carboxamide (410 mg, 1.0 mmol, 1.0 eq), 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (278 mg, 1.0 mmol, 1.0 eq) and K_2CO_3 (276 mg, 2.0 mmol, 2.0 eq) in DMF (10 mL) was stirred at 90 °C overnight. After cooled to rt, the mixture was poured into water. The precipitate was collected and dried to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indazole-3-carboxamide as a yellow solid (405 mg, 67%).

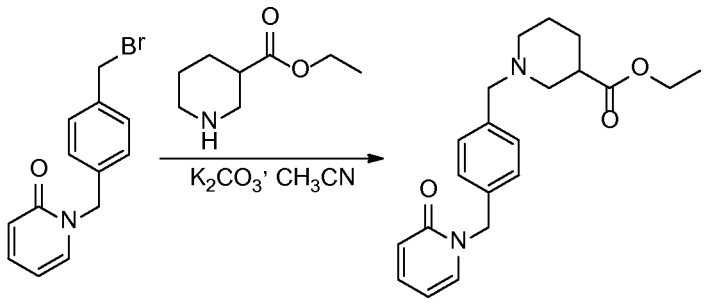


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indazole-3-carboxamide (405 mg, 0.67 mmol, 1.0 eq) in HCl/1,4-dioxane (~2 M, 10 mL) was stirred at rt overnight. The mixture was concentrated and the resulting residue was purified by preparative HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indazole-3-carboxamide as yellow solid. LCMS ($M+H^+$) m/z calculated 523.1, found 522.8. ^1H NMR (CD_3OD, 300 MHz) δ 8.26 (d, 1H), 7.96 (s, 1H), 7.61 (d, 1H), 7.56-7.46 (m, 3H), 7.40 (t, 1H), 7.35-7.25 (m, 2H), 7.22 (s, 4H), 6.54 (d, 1H), 6.35 (t, 1H), 5.67 (s, 2H), 5.13 (s, 2H), 4.96 (s, 2H).

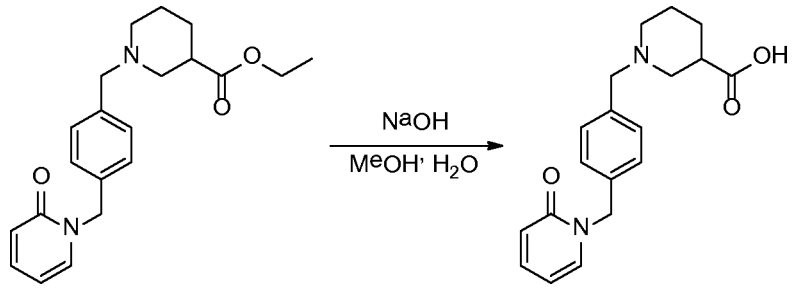
Example 9: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide



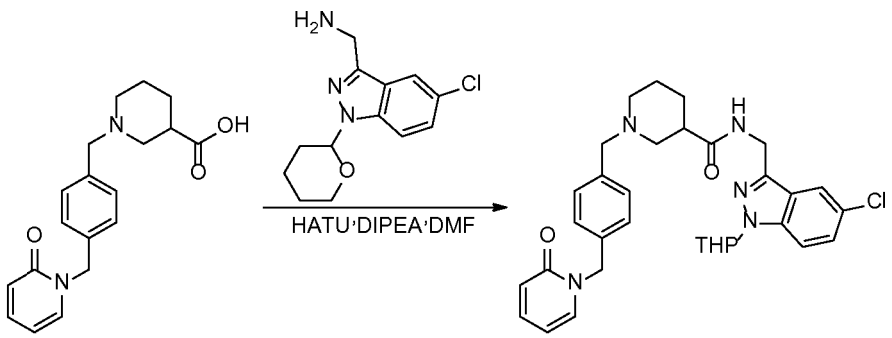
N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide



To a solution of 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (100 mg, 0.36 mmol, 1.0 eq) in CH_3CN (5 mL) were added K_2CO_3 (149 mg, 1.08 mmol, 3.0 eq) and ethyl piperidine-3-carboxylate (113 mg, 0.72 mmol, 2.0 eq). The mixture was heated at 80 °C overnight, and then concentrated. The resulting residue was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via flash chromatography to afford ethyl 1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxylate as a colorless oil (100 mg, 79%).

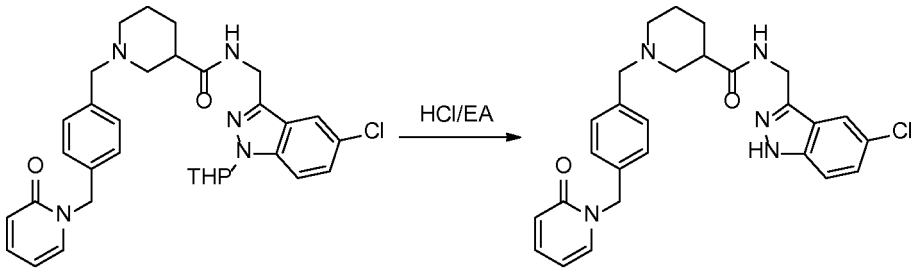


To a solution of ethyl 1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxylate (100 mg, 0.28 mmol, 1.0 eq) in MeOH (2 mL) and H_2O (2 mL) was added NaOH (34 mg, 0.85 mmol, 3.0 eq). The mixture was heated at 60 °C for 30 min. The mixture was concentrated to remove MeOH, then diluted with ice-water (10 mL) and acidified with 1 N HCl to pH 2~3. The mixture was concentrated under reduced pressure. The resulting residue was re-dissolved in MeOH (20 mL) and filtered. The filtrate was concentrated under reduced pressure to afford 1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxylic acid as a white solid (200 mg crude, quant.).



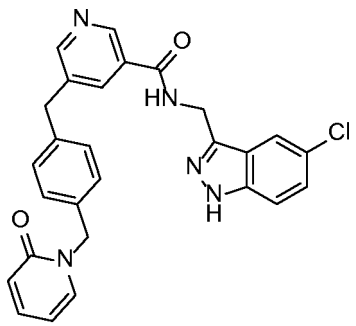
To a solution of 1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxylic acid (200 mg crude, 0.28 mmol, 1.0 eq) in DMF (5 mL) were added DIPEA (108 mg, 0.84 mmol, 3.0 eq) and HATU (128 mg, 0.34 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (82 mg, 0.31 mmol, 1.1 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL X

3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide as a white solid (70 mg, 43%).

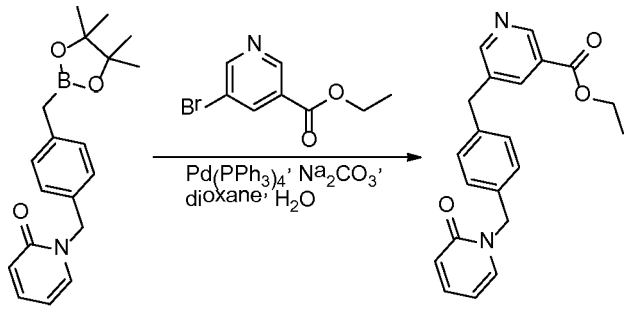


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide (70 mg, 0.12 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/EA (2 mL, 4 mmol) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure. The resulting residue was mixed with water (10 mL), neutralized with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide as an off-white solid (30 mg, 51%). LRMS ($M+H^+$) m/z caculated 490.2, found 489.9. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.07 (brs, 1 H), 8.40-8.50 (m, 1 H), 7.70-7.80 (m, 2 H), 7.51 (d, 1 H), 7.38-7.45 (m, 1 H), 7.30-7.35 (m, 1 H), 7.10-7.28 (m, 4 H), 6.41 (d, 1 H), 6.20-6.30 (m, 1 H), 5.05 (s, 2 H), 4.52 (d, 2 H), 3.40-3.45 (m, 2 H), 2.60-2.72 (m, 2 H), 2.30-2.40 (m, 1 H), 2.00-2.10 (m, 1 H), 1.80-1.95 (m, 1 H), 1.50-1.70 (m, 2 H), 1.30-1.48 (m, 2 H).

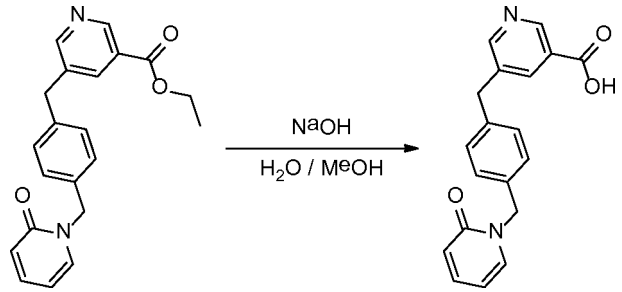
Example 10: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



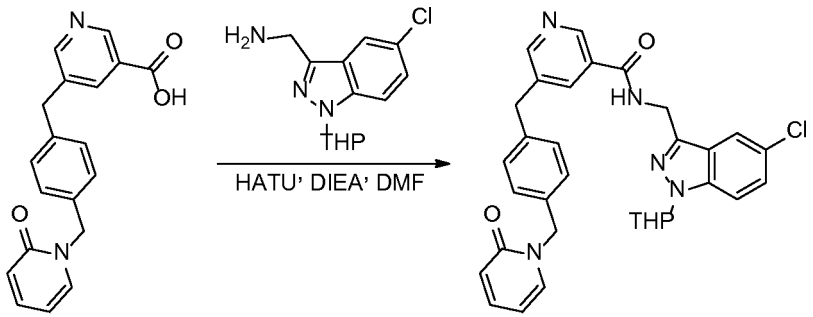
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



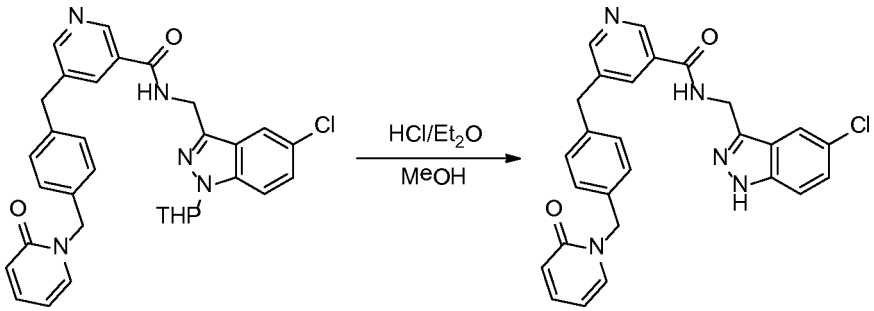
A mixture of 1-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzyl)pyridin-2(1H)-one (200 mg, 0.615 mmol, 1.0 eq), ethyl 5-bromonicotinate (170 mg, 0.738 mmol, 1.2 eq), $Pd(PPh_3)_4$ (71 mg, 0.061 mmol, 0.1 eq), Na_2CO_3 (196 mg, 1.84 mmol, 3.0 eq) in dioxane/H_2O (20 mL/2 mL) under N_2 was stirred at 95 °C overnight and concentrated. The residue was extracted with EA (50 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via flash chromatography (MeCN/H_2O = 30%-95%, v/v) to afford ethyl 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate as a colorless oil (71 mg, 33%).



To a solution of ethyl 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate (71 mg, 0.204 mmol, 1.0 eq) in MeOH (5 mL) was added drop wise a solution of NaOH (82 mg, 2.04 mmol, 10 eq) in water (3 mL). The mixture was stirred at rt overnight. The organic solvents were evaporated. To the residue was added conc. HCl till pH 5, then extracted with EA (20 mL ×3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid as a white solid (63 mg, 96%).

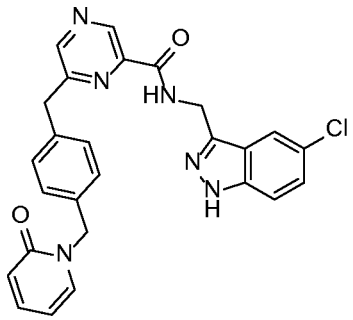


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (63 mg, 0.196 mmol, 1 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (63 mg, 0.236 mmol, 1.2 eq), HATU (82 mg, 0.216 mmol, 1.1 eq) and DIEA (51 mg, 0.393 mmol, 2 eq) in DMF (1 mL) was stirred at rt overnight. The mixture was poured into water (20 mL) and saturated $NaHCO_3$ (20 mL), extracted with EA (30 mL X 2). The combined organic layers was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow oil (72 mg, 64%).

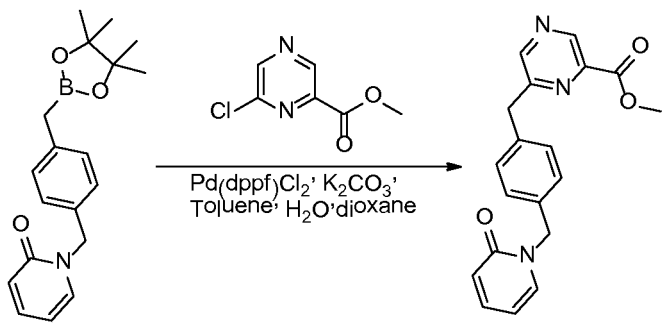


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (70 mg, 0.123 mmol, 1 eq) in MeOH (5 mL) and HCl/Et_2O (3 N, 5 mL) was stirred at rt overnight, then concentrated. The residue was collected and dried to afford the HCl salt of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (58 mg, 90%). LRMS ($M+H^+$) m/z calculated 484.2, found 484.2. ^1H NMR (DMSO-*d6*, 400 MHz) δ 13.09 (s, 1 H), 9.28 (t, 1 H), 8.85 (d, 1 H), 8.61 (d, 1 H), 8.04 (s, 1 H), 7.89 (d, 1 H), 7.73 (q, 1 H), 7.53 (d, 1 H) , 7.41-7.31 (m, 2 H), 7.24-7.19 (m, 4 H), 6.39 (d, 1 H), 6.20 (t, 1 H), 5.03 (s, 2 H), 4.77 (d, 2 H), 3.98 (s, 2 H).

Example 11: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrazine-2-carboxamide



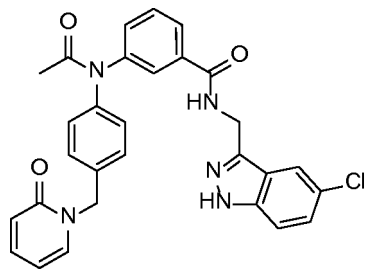
N-((5-chloro-1*H*-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)pyrazine-2-carboxamide



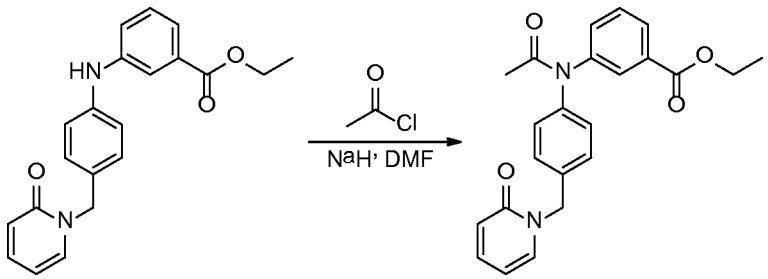
A mixture of 1-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzyl)pyridin-2(1H)-one (339 mg, 1.05 mmol, 3.0 eq), methyl 6-chloropyrazine-2-carboxylate (150 mg, 0.87 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (71 mg, 0.061 mmol, 0.1 eq), K_2CO_3 (240 mg, 1.74 mmol, 2.0 eq) in toluene/dioxane/H_2O (10 mL/1 mL/1 mL) under N_2 was stirred at 100 °C for 5 h and then concentrated. The residue was extracted with EA (50 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via pre-TLC to afford methyl 6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrazine-2-carboxylate as a white solid (100 mg, 34%).

N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrazine-2-carboxamide (HCl salt, 17.8 mg) was prepared from methyl 6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrazine-2-carboxylate as described for N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide. LRMS ($M+H^+$) m/z calculated 484.94, found 485.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.40 (t, 1 H), 9.03 (s, 1 H), 8.79 (s, 1 H), 7.72 (dd, 1 H), 7.53 (d, 1 H), 7.39 (t, 1 H), 7.36-7.22 (m, 4 H), 7.20 (d, 2H) , 6.38 (d, 1 H), 6.22-6.19 (t, 1 H), 5.03 (s, 2 H), 4.83 (d, 2 H), 4.19 (s, 2 H).

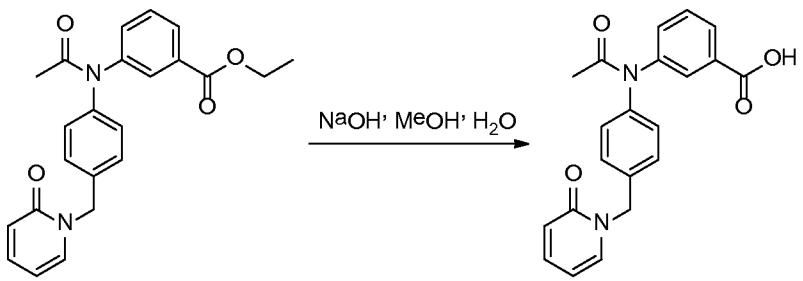
Example 12: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzamide



N-((5-chloro-1H-indazol-3-yl)methyl)-3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzamide

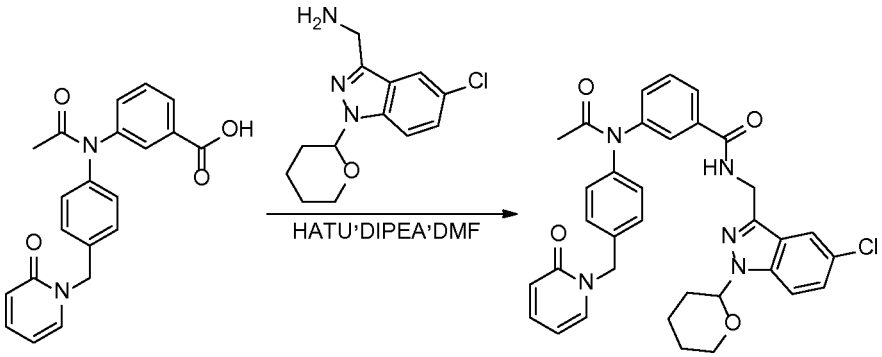


To a solution of ethyl 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzoate (230 mg, 0.66 mmol, 1.0 eq) in DMF (5 mL) was added NaH (79 mg, 60% in oil, 1.98 mmol, 3.0 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 15 min, then acetyl chloride (518 mg, 6.6 mmol, 10 eq) was added into the mixture. The reaction mixture was stirred at rt overnight. The reaction mixture was poured into ice-water (10 mL), extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford ethyl 3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzoate as a yellow solid (150 mg crude, 58%).

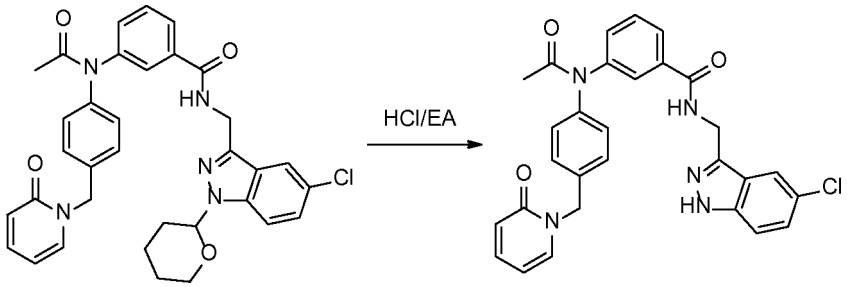


To a solution of ethyl 3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)-acetamido)benzoate (150 mg, 0.38 mmol, 1.0 eq) in MeOH (1 mL) and H_2O (1 mL) was added NaOH (46 mg, 1.15 mmol, 3.0 eq). The mixture was heated at 60 °C for 30 min. The mixture was concentrated to remove MeOH, then diluted with ice-water

(10 mL) and acidified with 1 N HCl to pH 3~4. The mixture was concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (20 mL) and filtered. The filtrate was concentrated under reduced pressure to afford 3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzoic acid as a yellow solid (300 mg crude, quant.).



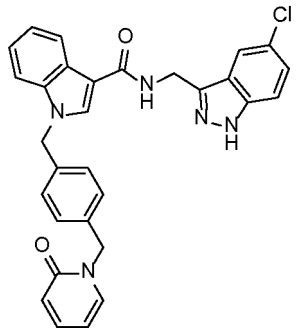
To a solution of 3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzoic acid (300 mg, 0.38 mmol, 1.0 eq) in DMF (3 mL) were added DIPEA (147 mg, 1.14 mmol, 3.0 eq) and HATU (173 mg, 0.46 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (111 mg, 0.42 mmol, 1.1 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzamide as a white solid (100 mg, 43%).



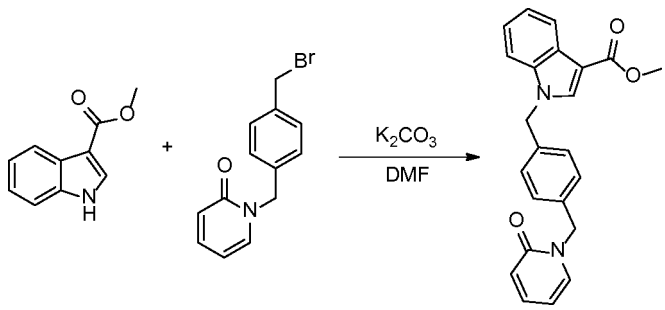
To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzamide (100 mg, 0.16 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/EA (2 mL, 4 mmol) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL), neutralized with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzamide as a white solid (70 mg, 83%). LRMS ($M+H^+$) m/z caculated 526.2, found 526.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.06 (brs, 1 H), 9.10-9.20 (m, 1 H), 7.90 (d, 1 H), 7.75-7.85 (m, 3 H), 7.20-7.60 (m, 9 H), 6.40 (d, 1 H), 6.20-6.30 (m, 1 H), 5.08 (s, 2 H), 4.76 (d, 2 H), 1.92 (s, 3 H).

Example 13: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-

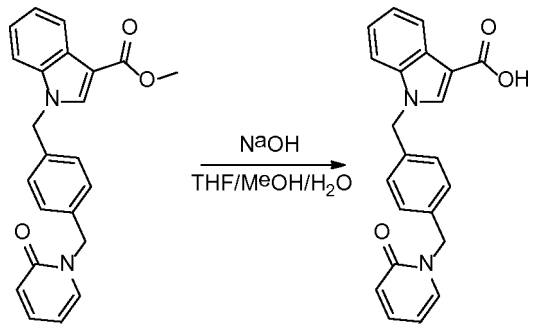
yl)methyl)benzyl)-1H-indole-3-carboxamide



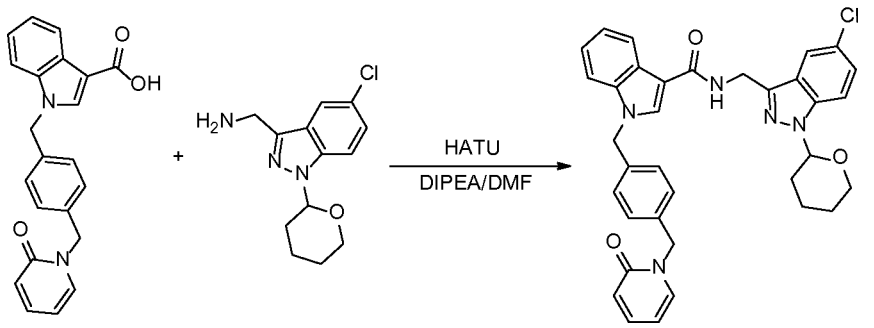
N-((5-chloro-1*H*-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)-1*H*-indole-3-carboxamide



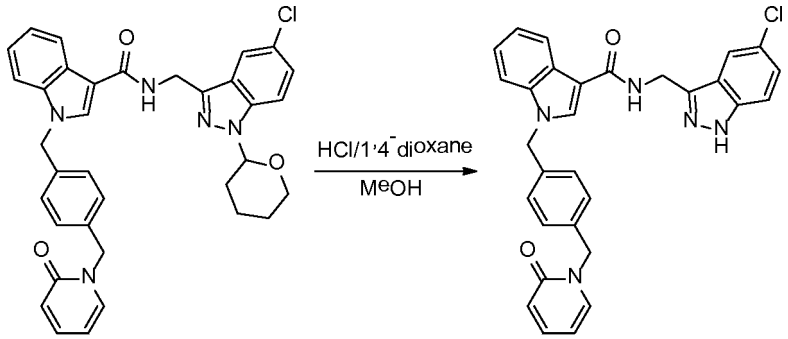
A mixture of methyl 1H-indole-3-carboxylate (263.5 mg, 1.5 mmol, 1.0 eq), 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (417.5 mg, 1.5 mmol, 1.0 eq) and K_2CO_3 (840 mg, 6 mmol, 4 eq) in DMF (5 mL) was stirred at 130 °C overnight. The mixture was mixed with water and extracted with DCM (20 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford methyl 1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxylate as a yellow solid (306 mg, 54.8%).



To a solution of methyl 1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxylate (306 mg, 0.82 mmol, 1.0 eq) in MeOH (10 mL) and THF (10 mL) was added a NaOH aqueous solution (4 N, 10 mL). The mixture was stirred at rt overnight. The organic solvents were evaporated. The resulting residue was acidified to pH 5 with HCl and extracted with DCM (20 mL X 5). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford 1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxylic acid as a yellow solid (290 mg, 98.6%).

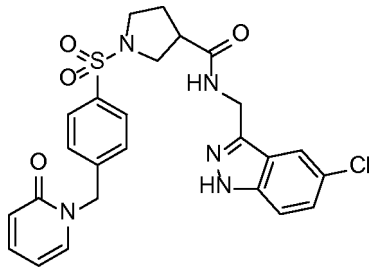


A mixture of 1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxylic acid (72 mg, 0.2 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (64 mg, 0.24 mmol, 1.2 eq), HATU (115 mg, 1.5 mmol, 1.5 eq) and DIPEA (0.8 mL) in DMF (5 mL) was stirred at 60 °C overnight. The mixture was mixed with water and extracted with DCM (10 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via prep-TLC (DCM/MeOH = 15/1, v/v) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxamide as a yellow solid (50 mg, 41%).

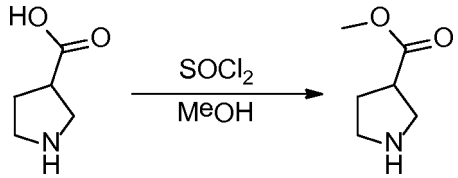


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxamide (50 mg, 0.083 mmol, 1 eq) in MeOH (2 mL) and HCl/dioxane (5 N, 2 mL) was stirred at rt overnight, then concentrated. The residue was suspended in $NaHCO_3$ solution and extracted with DCM (10 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via prep-TLC (DCM/MeOH = 15/1, v/v) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxamide as a white powder (27 mg, 62.6%). LRMS ($M+H^+$) m/z calculated 522.2, found 521.9. ^1H NMR (CD_3OD, 400 MHz) δ 8.20-8.18 (m, 1 H), 7.95-7.94 (m, 2 H), 7.65 (dd, 1 H), 7.54-7.49 (m, 2 H), 7.40-7.34 (m, 2 H) , 7.27-7.25 (m, 2 H) , 7.23-7.18 (m, 4 H) , 6.56 (d, 1 H) , 6.380 (t, 1 H), 5.42 (s, 2 H), 5.16 (s, 2 H), 4.94 (s, 2 H).

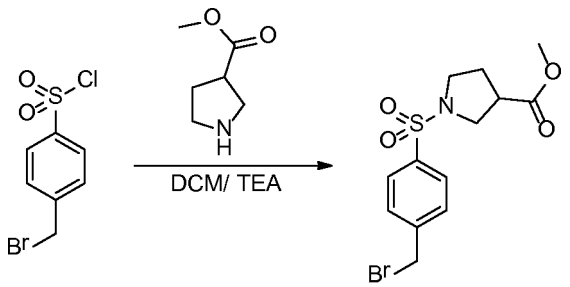
Example 14: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxamide



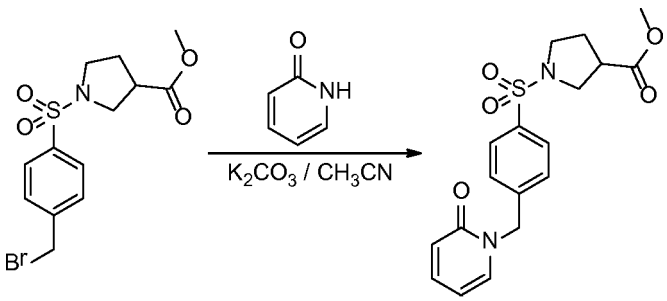
N-((5-chloro-1*H*-indazol-3-yl)methyl)-1-((4-((2-oxopyridin-1(2*H*)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxamide



To a solution of $SOCl_2$ (8.2 g, 70 mmol, 2.0 eq) in MeOH (80 mL) at 0 °C was added pyrrolidine-3-carboxylic acid (4 g, 35 mmol, 1.0 eq). The reaction mixture was stirred at 40 °C overnight, and then concentrated to afford methyl pyrrolidine-3-carboxylate as a yellow solid (4.4 g, quant.).

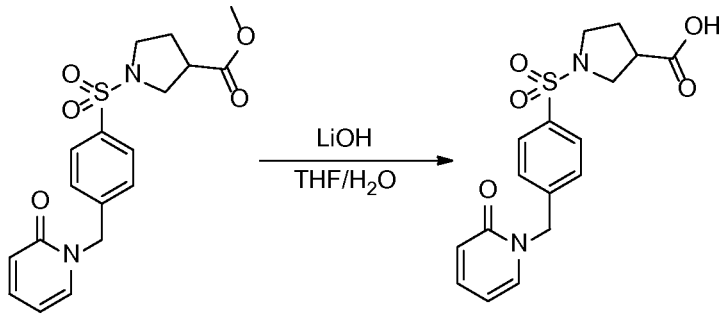


To a solution of 4-(bromomethyl)benzene-1-sulfonyl chloride (1.15 g, 4.26 mmol, 1.1 eq) in DCM (20 mL) was added TEA (1.17 g, 11.6 mmol, 3.0 eq). The reaction mixture was cooled to 0 °C, methyl pyrrolidine-3-carboxylate (0.5 g, 3.88 mmol, 1.0 eq) was then added. The reaction mixture was stirred at 0 °C for 0.5 h. The mixture was poured into water (20 mL) and extracted with EA (15 mL X 3). The organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified on silica gel column (PE/EA = 8/1 to 4/1, v/v) to afford methyl 1-((4-(bromomethyl)phenyl)sulfonyl)pyrrolidine-3-carboxylate as a yellow solid (300 mg, 21%).

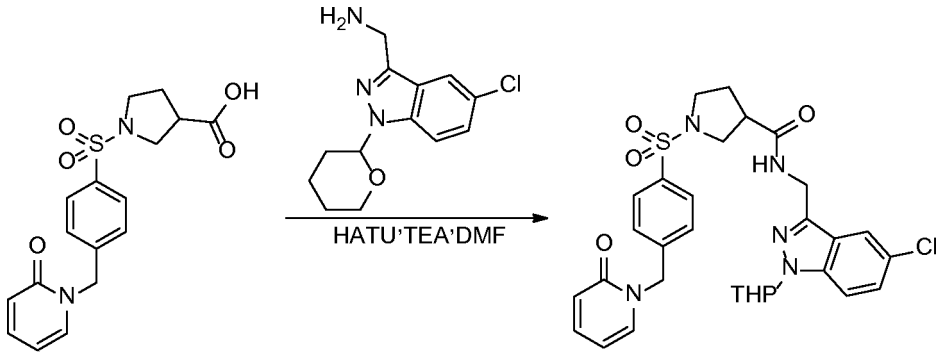


To a solution of methyl 1-((4-(bromomethyl)phenyl)sulfonyl)pyrrolidine-3-carboxylate (210 mg, 0.58 mmol, 1.0 eq) in CH_3CN (10 mL) were added K_2CO_3 (241 mg, 1.75 mmol, 3.0 eq) and pyridin-2(1H)-one (55 mg, 0.58 mmol, 1.0 eq). The mixture was stirred at 70 °C for 2 h. The mixture was poured into water (20 mL) and extracted with EA (15 mL X 3). The organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified on silica gel column (DCM/MeOH = 100/2, v/v) to afford methyl 1-

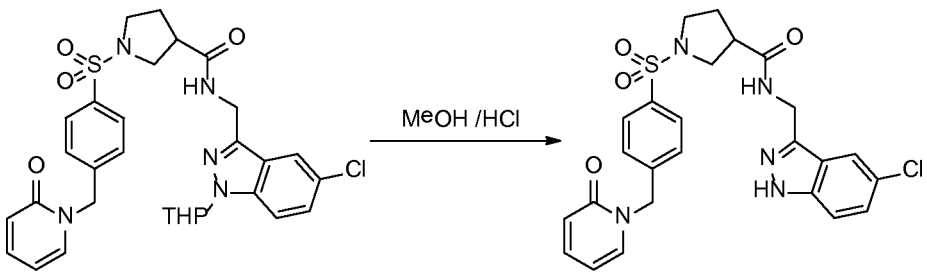
((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxylate as a white solid (160 mg, 73%).



To a solution of methyl 1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxylate (180 mg, 0.48 mmol, 1.0 eq) in THF/H_2O (6 mL/2 mL) was added LiOH (200 mg, 4.8 mmol, 3.0 eq). The mixture was stirred at rt overnight then concentrated to afford 1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxylic acid (173 mg, quant.).



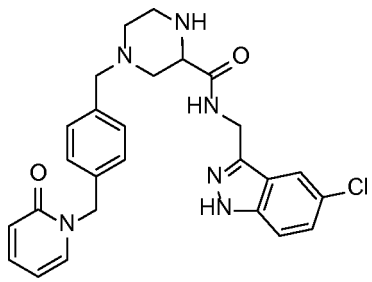
To a solution of 1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxylic acid (173 mg, 0.5 mmol, 1.0 eq) in DMF (10 mL) were added TEA (150 mg, 1.5 mmol, 3.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (132 mg, 0.5 mmol, 1.0 eq) and HATU (285 mg, 0.75 mmol, 1.5 eq). The reaction mixture was stirred at rtrt overnight. The mixture was mixed with water and extracted with EA. The EA extract was dried over Na_2SO_4 and concentrated. The residue was purified by Prep-HPLC to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxamide as a white solid (60 mg, 20%).



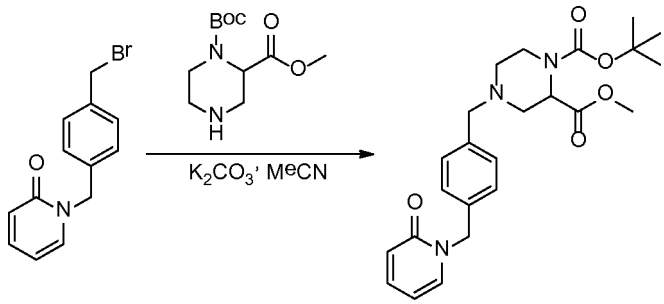
To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxamide (60 mg, 0.1 mmol, 1.0 eq) in MeOH (3 mL) was added HCl/MeOH (3 mL, 12 mmol). The mixture was stirred at rt overnight and then concentrated. The residue was purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxamide as a white solid (20 mg, 40%). LRMS ($M+H^+$) m/z calculated 526.01, found 526.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.50~8.51 (m, 1H), 7.81~7.84 (m, 2H),

7.73~7.76 (m, 2H), 7.54~7.46 (m, 4H), 7.34~7.37 (m, 1H), 6.56~6.60 (d, 1H), 6.39~6.44 (t, 1H), 5.29 (s, 2H), 4.62~4.85 (m, 2H), 3.50~3.56 (m, 1H), 3.31~3.33 (m, 3H), 2.84~2.89 (m, 1H), 1.92~1.96 (m, 2H).

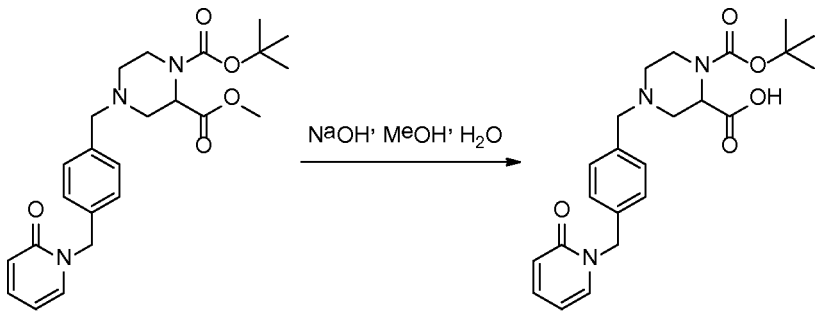
Example 15: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-2-carboxamide



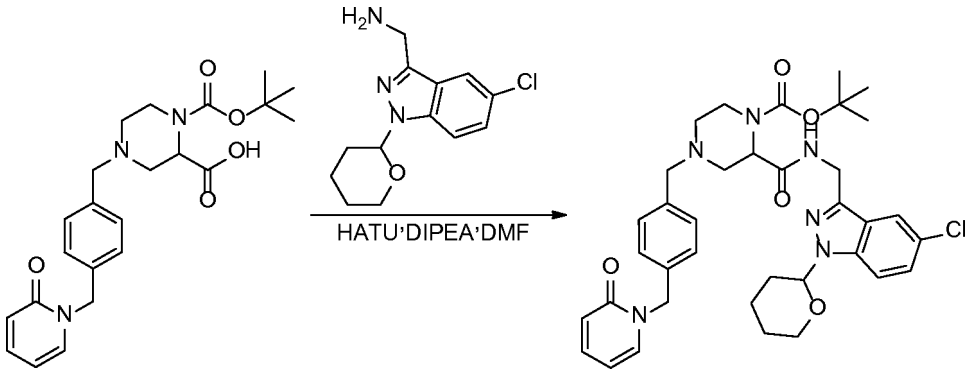
N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-2-carboxamide



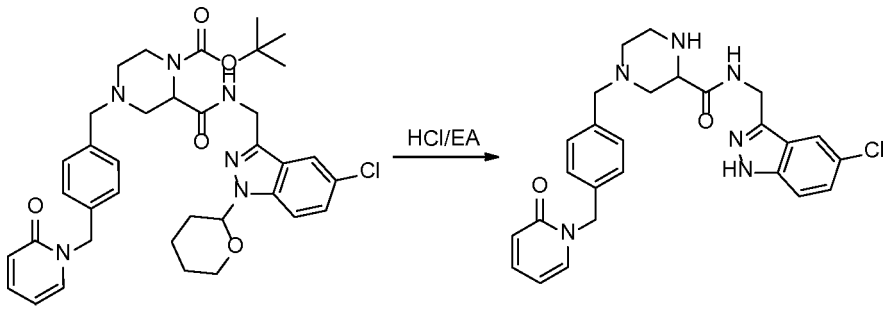
To a solution of 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (600 mg, 2.15 mmol, 1.0 eq) in CH_3CN (5 mL) were added K_2CO_3 (0.89 g, 6.45 mmol, 3.0 eq) and 1-tert-butyl 2-methyl piperazine-1,2-dicarboxylate (1.05 g, 4.32 mmol, 2.0 eq). The mixture was heated at 80 °C overnight, and then concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford 1-tert-butyl 2-methyl 4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1,2-dicarboxylate as a white solid (870 mg, 92%).



To a solution of 1-tert-butyl 2-methyl 4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1,2-dicarboxylate (150 mg, 0.34 mmol, 1.0 eq) in MeOH (5 mL) and H_2O (5 mL) was added NaOH (41 mg, 1.02 mmol, 3.0 eq). The mixture was heated at 60 °C for 30 min. The mixture was concentrated to remove MeOH, then diluted with ice-water (10 mL) and acidified with 1 N HCl to pH 5~6. The mixture was concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (20 mL) and filtered. The filtrate was concentrated under reduced pressure to afford 1-(tert-butoxycarbonyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-2-carboxylic acid as a white solid (300 mg crude, quant.).

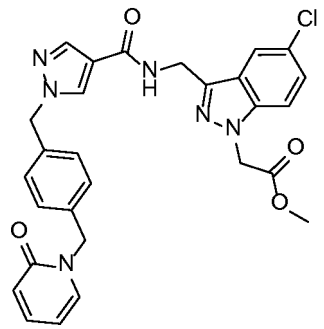


To a solution of 1-(tert-butoxycarbonyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-2-carboxylic acid (300 mg crude, 0.34 mmol, 1.0 eq) in DMF (5 mL) were added DIPEA (132 mg, 1.02 mmol, 3.0 eq) and HATU (155 mg, 0.41 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (99 mg, 0.37 mmol, 1.1 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford tert-butyl 2-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)carbamoyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1-carboxylate as a white solid (100 mg, 43%).

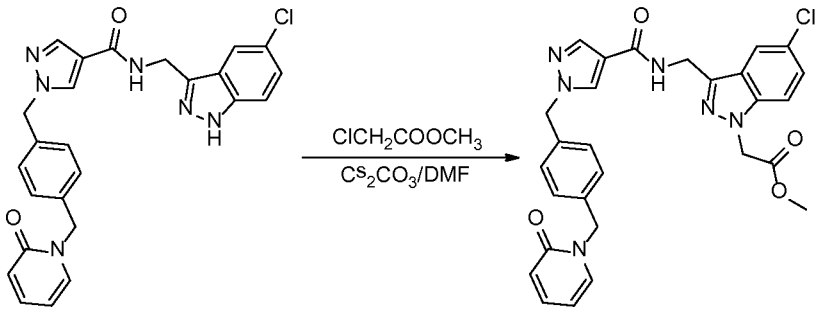


To a solution of tert-butyl 2-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)carbamoyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-1-carboxylate (100 mg, 0.15 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/EA (2 mL, 4 mmol) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL), neutralized with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-2-carboxamide as a white solid (20 mg, 27%). LRMS ($M+H^+$) m/z caculated 491.2, found 491.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.02 (brs, 1 H), 8.30-8.40 (m, 1 H), 7.85 (s, 1 H), 7.77 (d, 1 H), 7.51 (d, 1 H), 7.40-7.48 (m, 1 H), 7.33 (d, 1 H), 7.10-7.30 (m, 4 H), 6.41 (d, 1 H), 6.23 (t, 1 H), 5.06 (s, 2 H), 4.50-4.60 (m, 2 H), 3.30-3.45 (m, 4 H), 3.20-3.25 (m, 1 H), 2.70-2.85 (m, 1 H), 2.55-2.68 (m, 2 H), 1.90-2.00 (m, 2 H).

Example 16: Preparation of methyl 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetate

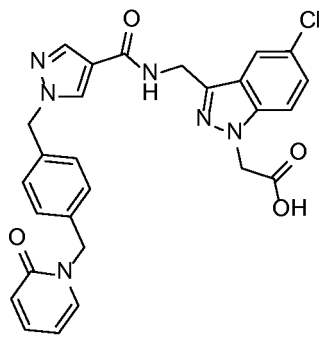


methyl 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)-1*H*-pyrazole-4-carboxamido)methyl)-1*H*-indazol-1-yl)acetate

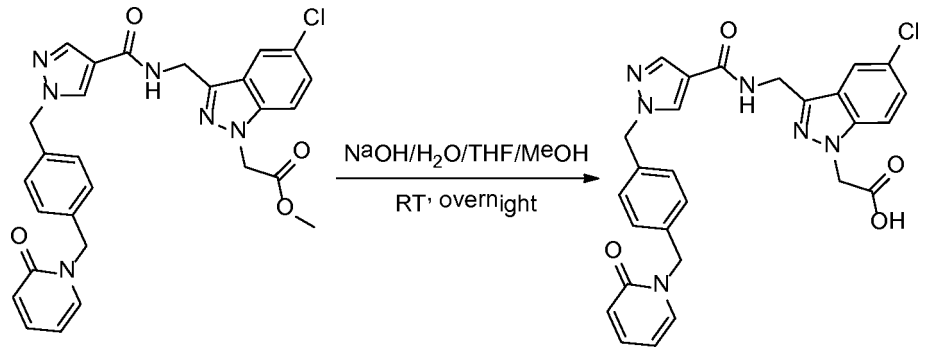


The mixture of N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide (94 mg, 0.2 mmol, 1.0 eq), methyl 2-chloroacetate (62 mg, 0.57 mmol, 2.9 eq) and Cs_2CO_3 (327 mg, 1 mmol, 5.0 eq) in DMF (3 mL) was stirred at 50 °C overnight. The mixture was poured into water and the precipitate was collected by suction and purified via prep-TLC (DCM:MeOH = 20:1, v/v) to afford methyl 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetate as a white powder (56 mg, quant.). LRMS ($M+H^+$) m/z calculated 545.2, found 545.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.15 (s, 1 H), 7.95 (s, 1 H), 7.88 (d, 1 H), 7.70 (dd, 1 H), 7.56-7.54 (m, 1 H), 7.51 (d, 1 H), 7.40 (dd, 1 H), 7.32 (d, 2 H), 7.27 (d, 2 H), 6.58 (d, 1 H) , 6.40 (t-d, 1 H), 5.36 (s, 2 H), 5.27 (s, 2 H), 5.20 (s, 2 H), 4.84 (s, 2 H), 3.77 (s, 3 H).

Example 17: Preparation of 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetic acid

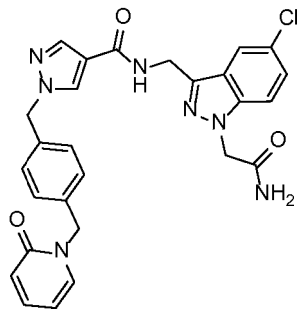


2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)-1*H*-pyrazole-4-carboxamido)methyl)-1*H*-indazol-1-yl)acetic acid

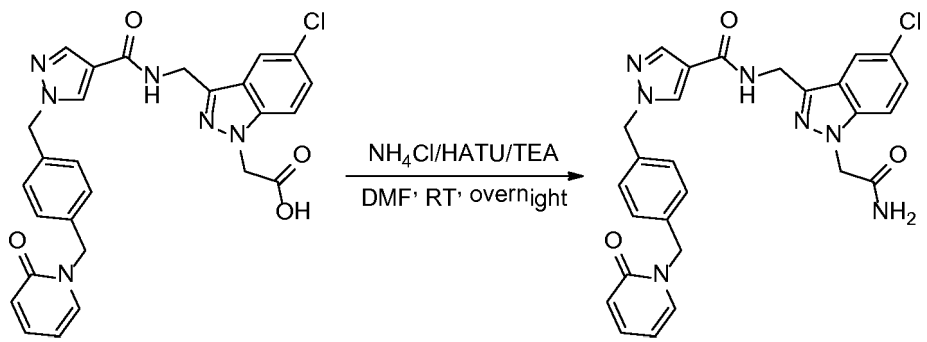


The mixture of methyl 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetate (230 mg, 0.42 mmol, 1.0 eq) and NaOH (34 mg, 0.85 mmol, 2.0 eq) in H_2O (1.5 mL), THF (1.5 mL) and MeOH (1.5 mL) was stirred at 25 °C overnight. The mixture was neutralized with 1 N HCl and the precipitate was collected by suction to afford 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetic acid as a yellow solid (160 mg, 72%). LCMS ($M-H^+$) m/z calculated 529.14, found 528.8. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.12 (brs, 1H), 8.75 (t, 1H), 8.27 (s, 1H), 7.90 (s, 2H), 7.73 (dd, 1H), 7.65 (d, 1H), 7.41-7.37 (m, 2H), 7.26-7.19 (m, 4H), 6.38 (d, 1H), 6.21 (t, 1H), 5.29 (s, 2H), 5.23 (s, 2H), 5.05 (s, 2H), 4.66 (d, 2H).

Example 18: Preparation of N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide



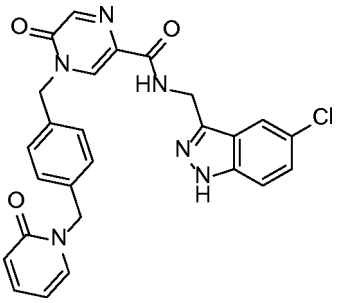
N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide



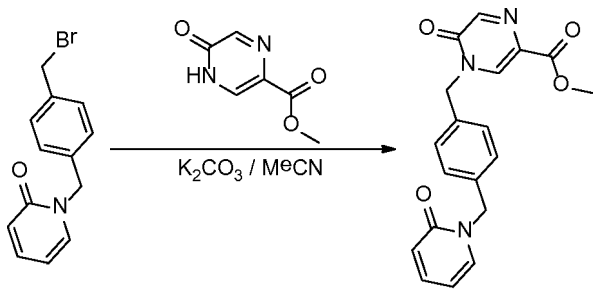
The mixture of 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetic acid (80 mg, 0.15 mmol, 1.0 eq), HATU (86 mg, 0.23 mmol, 1.5 eq), triethylamine (75 mg, 0.75 mmol, 5.0 eq) and NH_4Cl (16 mg, 0.30 mmol, 2.0 eq) in DMF (3 mL) was stirred at 25 °C overnight. The mixture was poured into water and the precipitate was collected by suction and purified via prep-HPLC to afford N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-

oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide as a white powder (5.4 mg, 7%). LCMS ($M+H^+$) m/z calculated 530.17, found 530.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.72 (t, 1H), 8.27 (s, 1H), 7.89 (s, 1H), 7.88 (d, 1H), 7.74 (dd, 1H), 7.61-7.58 (m, 2H), 7.43-7.35 (m, 2H), 7.29-7.19 (m, 4H), 6.38 (d, 2H), 6.21 (td, 1H), 5.29 (s, 2 H), 5.05 (s, 2H), 5.01 (s, 2H), 4.66 (d, 2H).

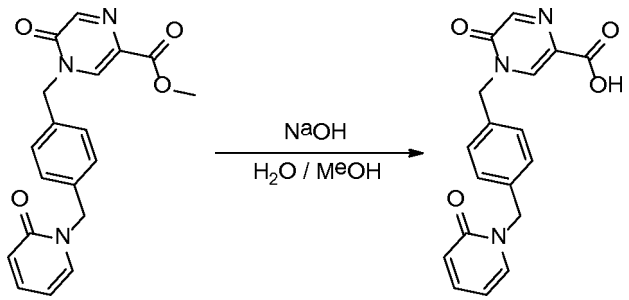
Example 19: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxamide



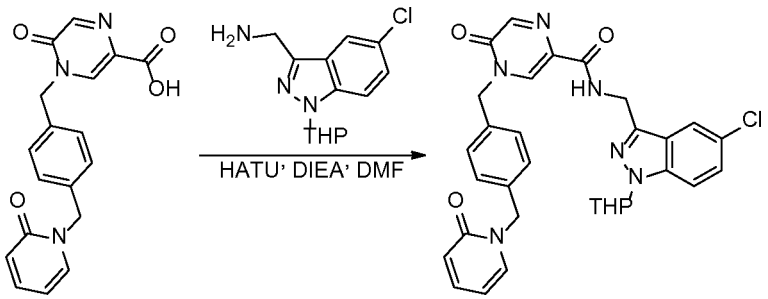
N-((5-chloro-1H-indazol-3-yl)methyl)-5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxamide



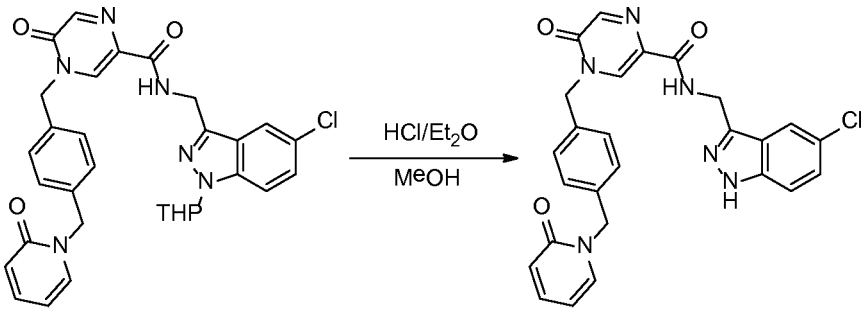
A mixture of 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (200 mg, 0.719 mmol, 1.0 eq), methyl 5-oxo-4,5-dihydropyrazine-2-carboxylate (133 mg, 0.863 mmol, 1.2 eq), K_2CO_3 (198 mg, 1.43 mmol, 2.0 eq) in MeCN (5 mL) was stirred at 85 °C under N_2 overnight and concentrated. The residue was mixed with water (20 mL), extracted with EA (30 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via flash chromatography (MeCN/H_2O = 30%-95%, v/v) to afford methyl 5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxylate as a white solid (169 mg, 66%).



To a solution of methyl 5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxylate (160 mg, 0.455 mmol, 1.0 eq) in MeOH (10 mL) was added drop wise a solution of NaOH (182 mg, 4.55 mmol, 10.0 eq) in water (5 mL). The mixture was stirred at rt overnight. The organic solvents were evaporated. To the residue was added conc. HCl till pH 3; the precipitate was collected and dried to afford 5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxylic acid (126 mg, 82%).

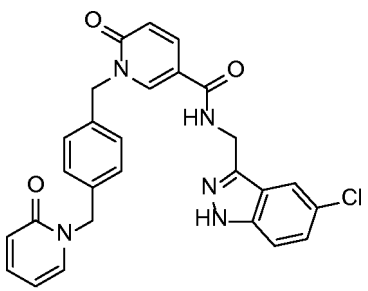


A mixture of 5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxylic acid (120 mg, 0.356 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (94 mg, 0.356 mmol, 1.0 eq), HATU (149 mg, 0.391 mmol, 1.1 eq) and DIEA (92 mg, 0.712 mmol, 2 eq) in DMF (3 mL) was stirred at rt for 3 hours. The mixture was poured into aqueous saturated $NaHCO_3$ (30 mL), extracted with EA (30 mL X 2). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxamide as a white solid (116 mg, 55%).

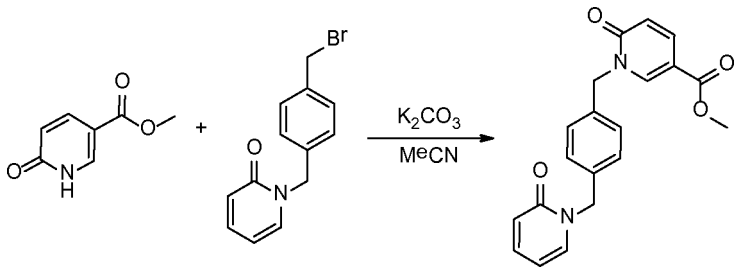


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxamide (110 mg, 0.188 mmol, 1 eq) in MeOH (5 mL) and HCl/Et_2O (3 N, 5 mL) was stirred at rt overnight. The precipitate was collected and dried to afford the HCl salt of N-((5-chloro-1H-indazol-3-yl)methyl)-5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxamide as a white solid (23 mg, 22%). LRMS ($M+H^+$) m/z calculated 501.2, found 501.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.02 (s, 1 H), 9.01-8.99 (m, 1 H), 8.51 (s, 1 H), 8.01-7.99 (m, 2 H), 7.76-7.74 (m, 1 H), 7.53-7.49 (m, 1 H), 7.47-7.23 (m, 6 H), 6.38 (d, 1 H), 6.31 (t, 1 H), 5.14 (s, 2 H), 5.05 (s, 2 H), 4.73 (d, 2 H).

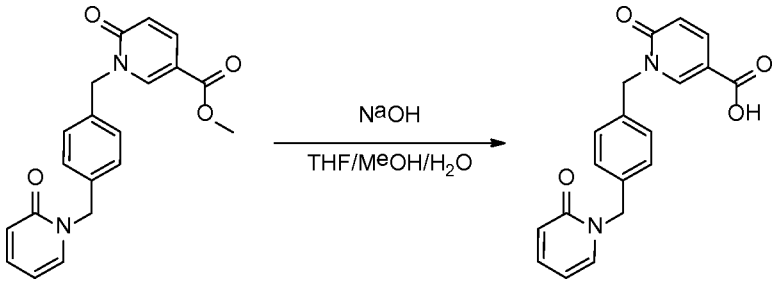
Example 20: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxamide



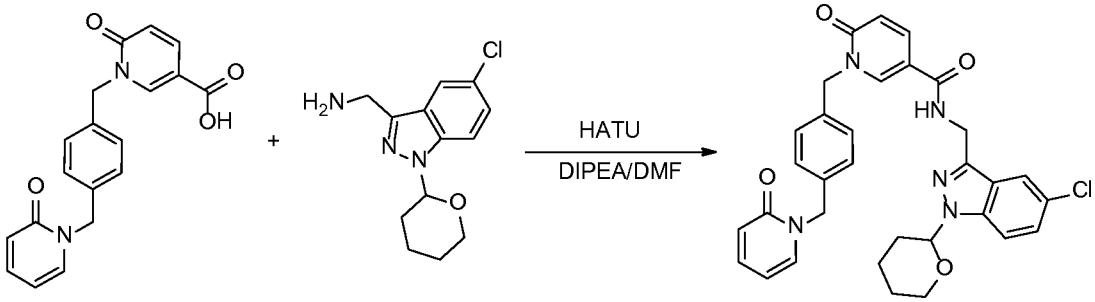
N-((5-chloro-1*H*-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxamide



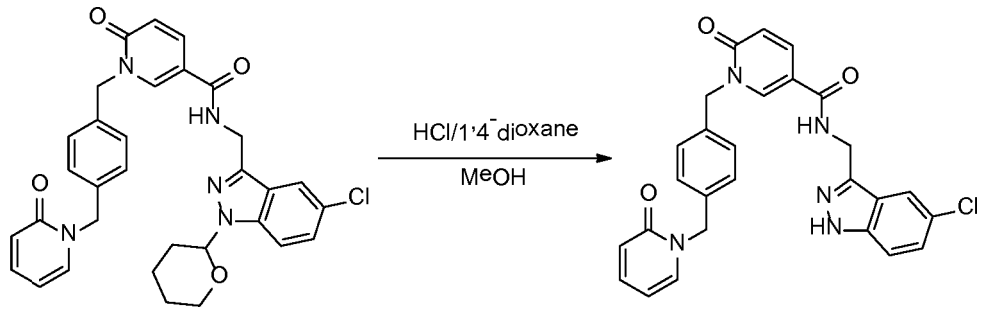
A mixture of methyl 6-oxo-1,6-dihydropyridine-3-carboxylate (115 mg, 0.75 mmol, 1.05 eq), 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (198 mg, 0.71 mmol, 1.0 eq) and K_2CO_3 (220 mg, 1.6 mmol, 2.2 eq) in MeCN (5 mL) was stirred at 85 °C overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified via flash chromatography to afford methyl 6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxylate as a white solid (214 mg, 85.9%).



To a solution of methyl 6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxylate (214 mg, 0.61 mmol, 1.0 eq) in MeOH (10 mL) and THF (10 mL) was added a 2 N NaOH aqueous solution (10 mL). The mixture was stirred at rt overnight. The organic solvents were evaporated. The residue was adjusted to pH 2 with HCl and filtered. The solid was collected to afford 6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxylic acid as a white solid (200 mg, 97.6%).

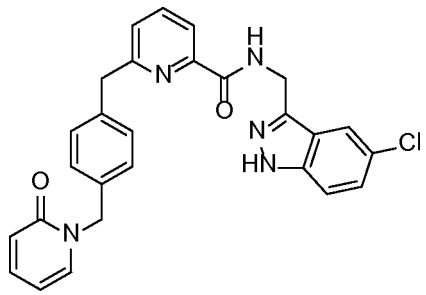


A mixture of 6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxylic acid (85 mg, 0.25 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (80 mg, 0.30 mmol, 1.2 eq), HATU (124 mg, 0.32 mmol, 1.3 eq) and DIPEA (1 mL) in DMF (4 mL) was stirred at 55 °C overnight. The mixture was concentrated and the residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxamide as a yellow solid (115 mg, 78.2%).

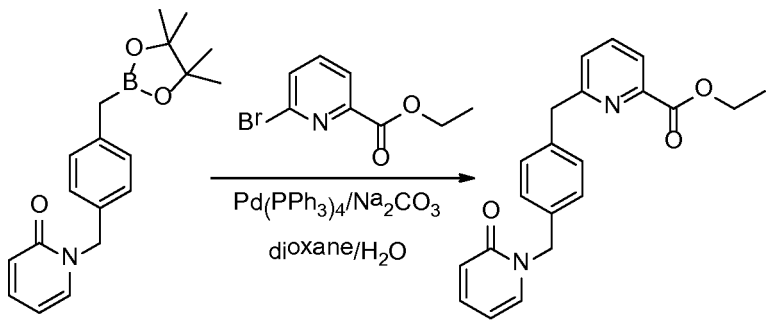


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxamide (115 mg, 0.197 mmol, 1 eq) in MeOH (3 mL) and HCl/dioxane (5 N, 3 mL) was stirred at rt overnight, then diluted with DCM (10 mL). The mixture was filtered and the solid was washed with DCM to afford the HCl salt of N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxamide as a yellow solid (84 mg, 79.5%). LRMS ($M+H^+$) m/z calculated 500.1, found 500.2. ^1H NMR (CD_3OD, 300 MHz) δ 8.42-8.40 (m, 1 H), 8.00-7.94 (m, 2 H), 7.87-7.86 (m, 1 H), 7.84-7.78 (m, 1 H), 7.51 (d, 1 H) , 7.40-7.31 (m, 5 H), 6.83 (d, 1 H) , 6.75 (t-d, 1 H), 6.57 (d, 1 H) , 5.33 (s, 2 H), 5.22 (s, 2 H), 4.87 (s, 2 H).

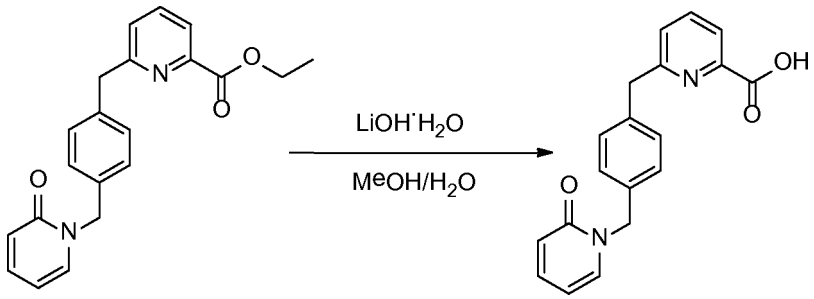
Example 21: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide



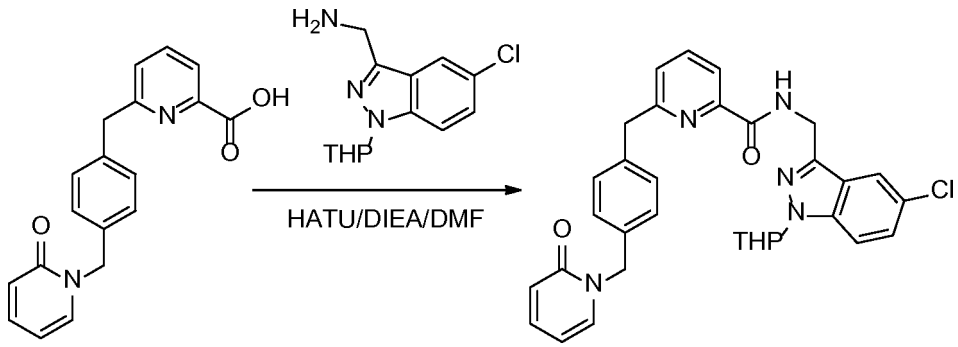
N-((5-chloro-1*H*-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)picolinamide



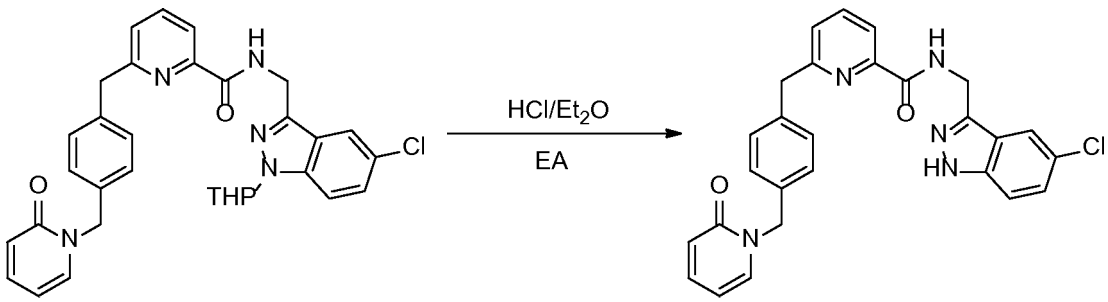
A mixture of 1-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzyl)pyridin-2(1H)-one (200 mg, 0.61 mmol, 1.0 eq), ethyl 6-bromopicolinate (170 mg, 0.73 mmol, 1.2 eq), Na_2CO_3 (196 mg, 1.8 mmol, 3.0 eq) and $Pd(PPh_3)_4$ (71 mg, 0.06 mmol, 0.1 eq) in dioxane/H_2O (20 mL/2 mL) was stirred at 95 °C under N_2 overnight. After cooled to rt, the mixture was filtered. The filtrate was concentrated. The residue was purified on silica gel column (PE/EtOAc = 1/1) to afford ethyl 6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinate as a yellow oil (62 mg, 28%).



To a solution of ethyl 6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinate (45 mg, 0.12 mmol, 1.0 eq) in MeOH (2 mL) and H_2O (1 mL) was added LiOH.H_2O (16 mg, 0.38 mmol, 3.0 eq). The mixture was stirred at 70 °C for 2 h. The organic solvents were evaporated. The residue was acidified with conc HCl to pH 5 and extracted with EA (3x20 mL), the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinic acid as a white solid (32 mg, 77%).

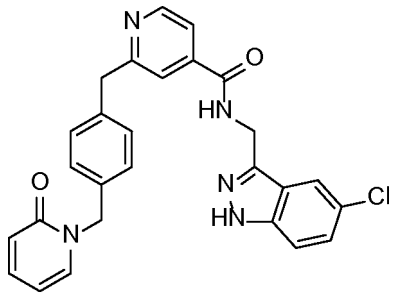


A mixture of 6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinic acid (32 mg, 0.10 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (31.8 mg, 0.12 mmol, 1.2 eq), HATU (46 mg, 0.12 mmol, 1.2 eq) and DIEA (39 mg, 0.30 mmol, 3.0 eq) in DMF (2 mL) was stirred at rt for 3 h. The mixture was purified by flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide as a white solid (21 mg, 37%).

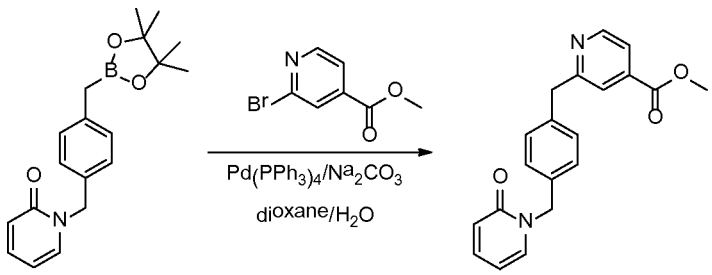


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide (21 mg, 0.03 mmol, 1.0 eq) in EA (5 mL) and HCl/Et_2O (3 N, 2 mL) was stirred at rt for 20 h. Then the mixture was evaporated under reduced pressure to afford N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide as a white solid (11 mg, 57%). LRMS ($M+H^+$) m/z calculated 484.1, found 484.1. ^{1}H NMR (MeOH-*d4*, 400 MHz) δ 7.84 (d, 1H), 7.77 (d, 1H), 7.72 (t, 1H), 7.51 (m, 1H), 7.41-7.37 (m, 2H), 7.26-7.22 (m, 2H), 7.16 (d, 2H), 7.09 (d, 2H), 6.44 (d, 1H), 6.24 (t, 1H), 5.02 (s, 2H), 4.83 (s, 2H), 4.05 (s, 2H).

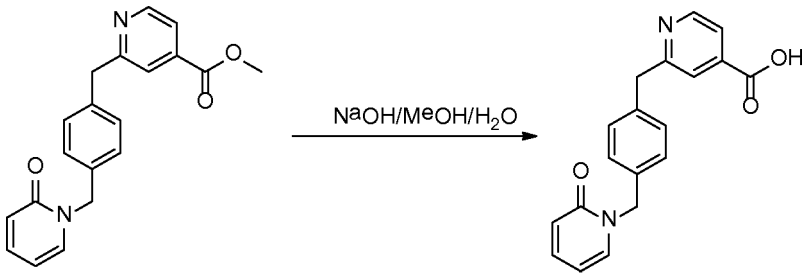
Example 22: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



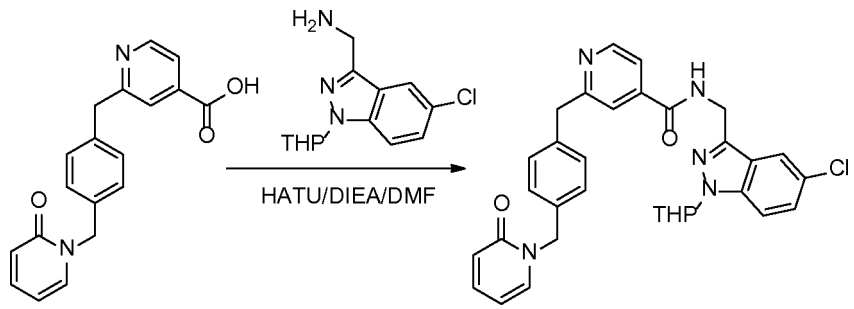
N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



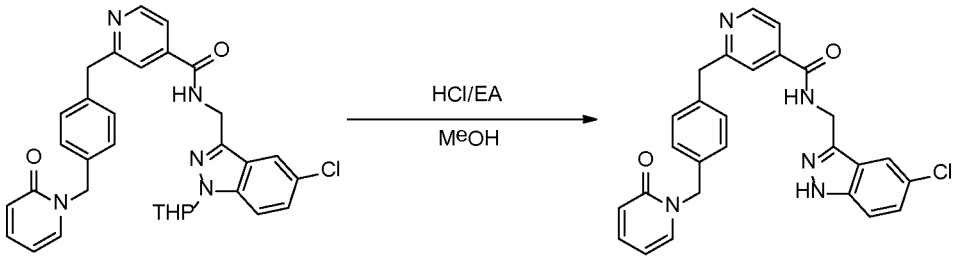
A mixture of 1-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzyl)pyridin-2(1H)-one (200 mg, 0.61 mmol, 1.0 eq), methyl 2-bromoisonicotinate (159 mg, 0.73 mmol, 1.2 eq), Na_2CO_3 (196 mg, 1.8 mmol, 3.0 eq) and $Pd(PPh_3)_4$ (71 mg, 0.06 mmol, 0.1 eq) in dioxane/H_2O (20 mL/2 mL) was stirred at 95 °C under N_2 overnight. After cooled to rt, the mixture was filtered. The filtrate was concentrated. The residue was purified on silica gel column (PE/EtOAc = 1/1) to afford methyl 2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinate as a yellow oil (72 mg, 35%).



To a solution of methyl 2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinate (70 mg, 0.20 mmol, 1.0 eq) in MeOH (6 mL) and H_2O (4 mL) was added NaOH (82 mg, 2.0 mmol, 10.0 eq). The mixture was stirred at 70 °C for 1 h. The organic solvents were evaporated. The residue was acidified with conc HCl to pH 5 and extracted with EA (3x20 mL), the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinic acid as a white solid (64 mg, 95%).

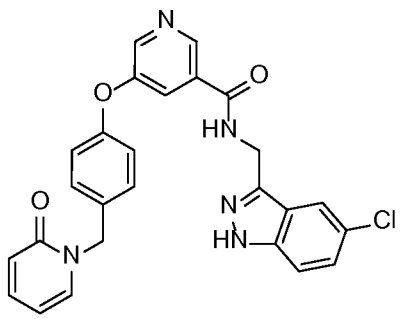


A mixture of 2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinic acid (64 mg, 0.19 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (63 mg, 0.23 mmol, 1.2 eq), HATU (82 mg, 0.21 mmol, 1.1 eq) and DIEA (51 mg, 0.39 mmol, 2.0 eq) in DMF (1 mL) was stirred at rt overnight. The mixture was poured into water (25 mL), extracted with EA (2x40 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was then further purified by flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide as a brown oil (70 mg, 61%).

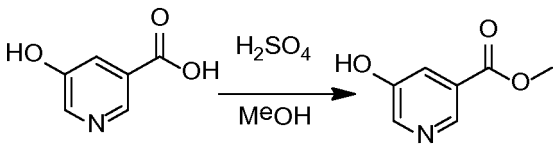


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (70 mg, 0.12 mmol, 1.0 eq) in EA (5 mL) and HCl/Et_2O (5 N, 5 mL) was stirred at rt for 20 h. Then the mixture was concentrated. The residue was purified by flash chromatography (MeCN/H_2O = 1/2 to 9/1) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide as a white solid (21 mg, 35%). LRMS ($M+H^+$) m/z calculated 484.1, found 484.1. ^1H NMR (MeOH-*d4*, 400 MHz) δ 8.43 (d, 1H), 7.73 (s, 1H), 7.54-7.48 (m, 3H), 7.39-7.34 (m, 2H), 7.22 (d, 1H), 7.11 (m, 4H), 6.43 (d, 1H) , 6.23 (t, 1H), 5.01 (s, 2H), 4.76 (s, 2H), 4.03 (s, 2H).

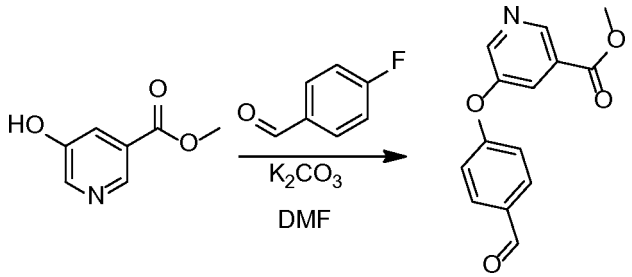
Example 23: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinamide



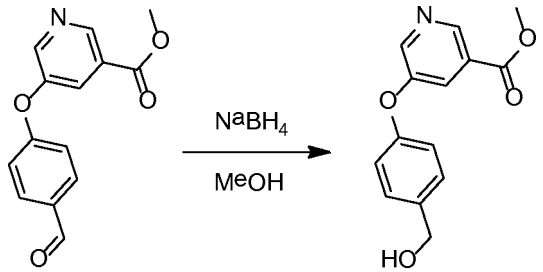
N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)phenoxy)nicotinamide



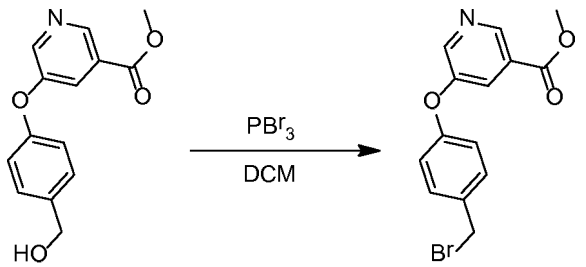
A mixture of 5-hydroxynicotinic acid (3 g, 21.6 mmol), conc H_2SO_4 (2.2 g, 21.6 mmol) in MeOH (50 mL) was heat at 70 °C overnight. The mixture was concentrated, poured into water (100 mL) and extracted with EA (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford methyl 5-hydroxynicotinate as a white solid (2.3 g, 71%).



A mixture of methyl 5-hydroxynicotinate (2 g, 0.01 mol), 4-fluorobenzaldehyde (2.1 g, 0.13 mol) and K_2CO_3 (3.6 g, 0.02 mol) in DMF (50 mL) was heated at 70 °C for overnight. The mixture was diluted with water (100 mL) and extracted with EA (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Purification by flash chromatography (PE/EA = 6/1, v/v) afforded methyl 5-(4-formylphenoxy)nicotinate as a yellow solid (2.2 g, 65%).

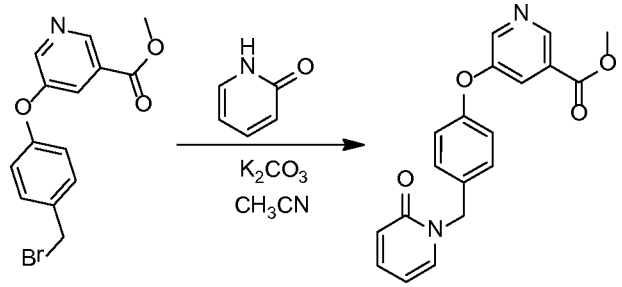


A mixture of methyl 5-(4-formylphenoxy)nicotinate (1.5 g, 5.76 mmol) and $NaBH_4$ (218 mg, 5.76 mmol) in MeOH (20 mL) was stirred at rt for 10 min. The reaction was quenched with aq NH_4Cl (10 mL). The mixture was concentrated, poured into water (100 mL) and extracted with EA (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Purification by flash chromatography (PE/EA = 1/1, v/v) afforded methyl 5-(4-(hydroxymethyl)phenoxy)nicotinate as a yellow solid (1.48 g, 64%).

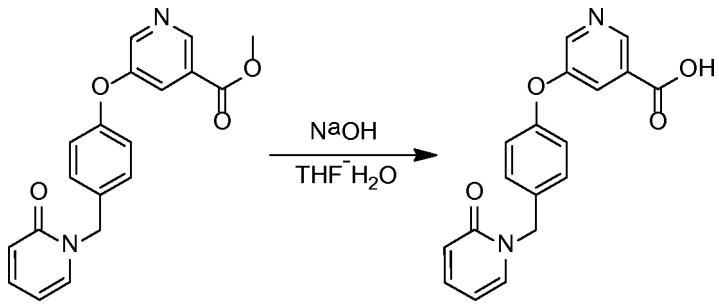


A solution of methyl 5-(4-(hydroxymethyl)phenoxy)nicotinate (500 mg, 1.92 mmol), PBr_3 (785 mg, 2.90 mmol) in DCM (5 mL) was stirred at rt for 2 h. The mixture was diluted with water (100 mL) and extracted

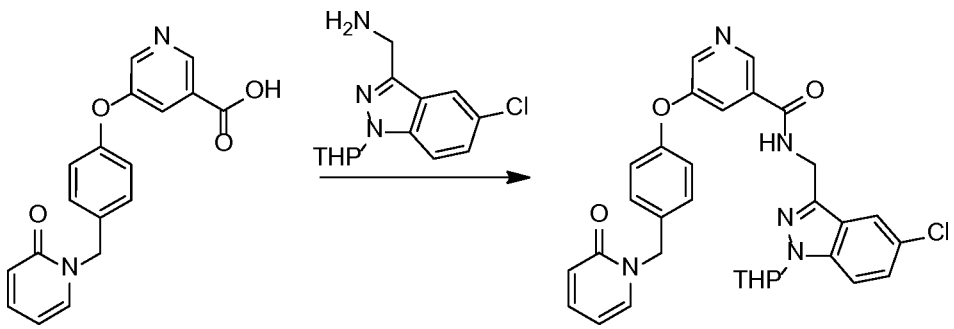
with EA (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford methyl 5-(4-(bromomethyl)phenoxy)nicotinate (500 mg, 70%).



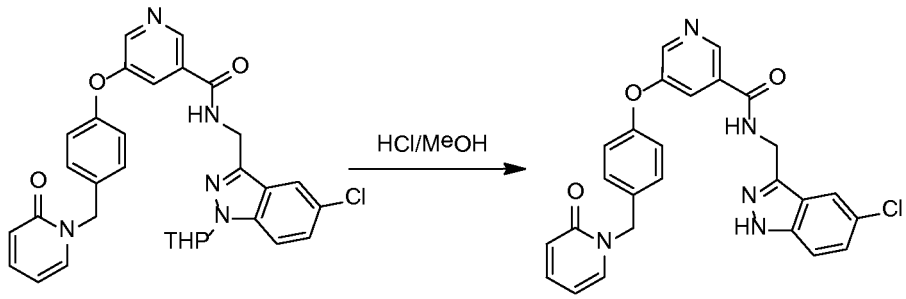
A mixture of methyl 5-(4-(bromomethyl)phenoxy)nicotinate (630 mg, 2.3 mmol), pyridin-2(1H)-one (238 mg, 2.5 mmol) and K_2CO_3 (952 mg, 7 mmol) in CH_3CN (10 mL) was heated at 80 °C for overnight. The mixture was diluted with water (100 mL) and extracted with EA (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Purification by flash chromatography (PE/EA = 1/1, v/v) afforded methyl 5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinate (150 mg, 30%).



A mixture of methyl 5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinate (90 mg, 0.34 mmol) and NaOH (200 mg, 0.51 mmol) in THF/H_2O (4 mL / 1 mL) was stirred at rt for 2 h. The mixture was concentrated to afford 5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinic acid (50 mg, 80%) which was used directly withtout further purification.

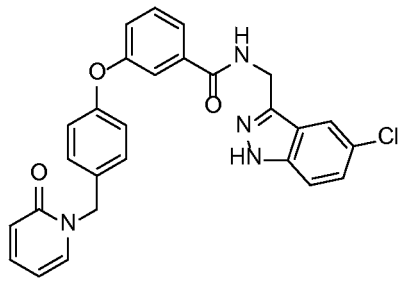


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinic acid (40 mg, 0.12 mmol), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (33 mg, 0.12 mmol) and TEA (38 mg, 0.37 mmol), HATU (71 mg, 0.18 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was diluted with water (100 mL) and extracted with EA (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Purification by flash chromatography (PE/EA = 1/1, v/v) afforded N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinamide as a white solid (50 mg, 73%).

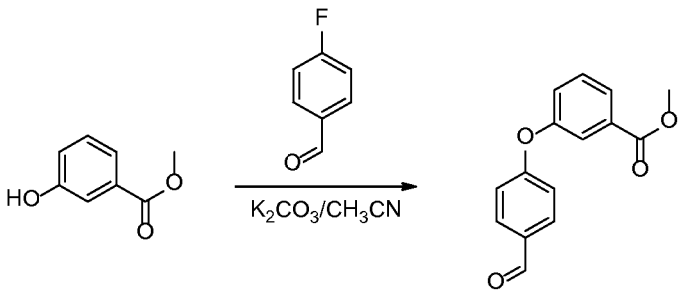


A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinamide (50 mg, 0.09 mmol) in HCl/MeOH (5 mL) was stirred at rt overnight. The mixture was concentrated and purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinamide as a white solid (13 mg, 31%). LRMS ($M+H^+$) m/z calculated 486, found 486.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.12 (s, 1 H), 8.81 (s, 1 H), 8.58 (s, 1 H), 8.14-8.13 (d, 1 H), 7.92 (s, 1 H), 7.91-7.89 (m, 1 H), 7.57-7.53 (m, 3 H), 7.42-7.39 (m, 1 H), 7.31-7.29 (d, 2 H), 6.92-6.90 (d, 1 H), 6.85-6.82 (m, 1 H), 5.42 (s, 2 H), 4.96 (s, 2 H).

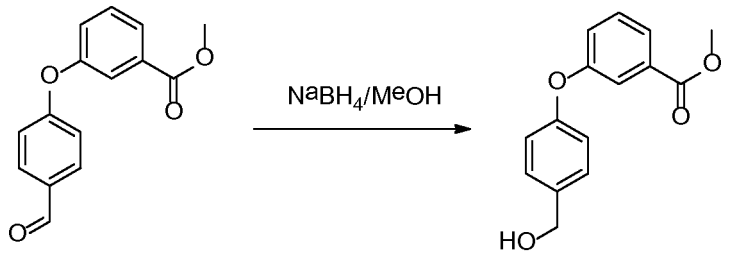
Example 24: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzamide



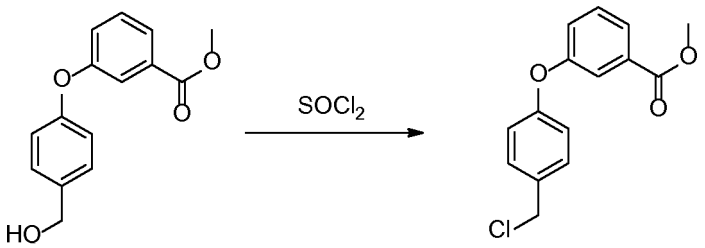
N-((5-chloro-1*H*-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2*H*)-yl)methyl)phenoxy)benzamide



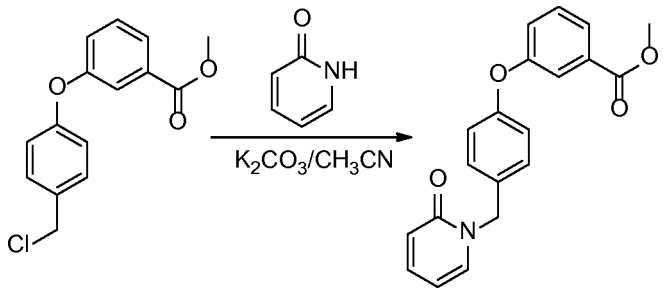
The mixture of methyl 3-hydroxybenzoate (2 g, 13.2 mmol, 1.0 eq), 4-fluorobenzaldehyde (1.6 g, 13.2 mmol, 1.0 eq) and K_2CO_3 (3.6 g, 26.4 mmol, 2.0 eq) in CH_3CN (50 mL) was stirred at 80 °C overnight. Then the mixture was cooled to rt and filtered. The filtrate was concentrated. The residue was purified on silica gel column (PE/EtOAc = 5/1) to afford methyl 3-(4-formylphenoxy)benzoate as a colorless oil (1.7 g, 50%).



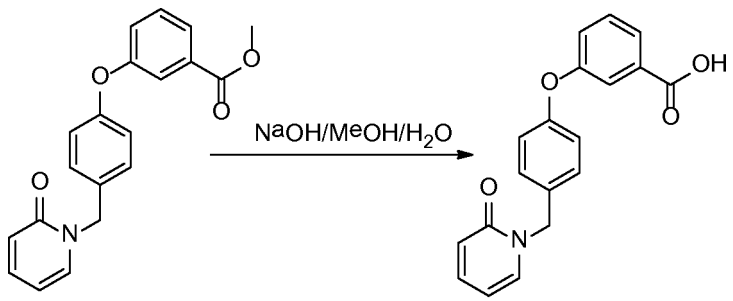
To a solution of methyl 3-(4-formylphenoxy)benzoate (1.7 g, 6.64 mmol, 1.0 eq) in MeOH (20 mL) was added $NaBH_4$ (505 mg, 13.3 mmol, 2.0 eq) at 0 °C. The mixture was stirred at rt for 2 h. LCMS showed the reaction complete. Then the mixture was concentrated, diluted with EtOAc (50 mL). The mixture was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (PE/EtOAc = 5/1) to give methyl 3-(4-(hydroxymethyl)phenoxy)benzoate as a yellow oil (680 mg, 40%).



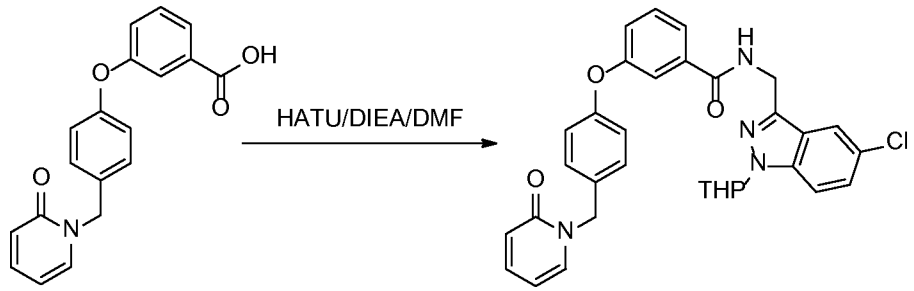
The mixture of methyl 3-(4-(hydroxymethyl)phenoxy)benzoate (680 mg, 2.6 mmol, 1.0 eq) in $SOCl_2$ (10 mL) was refluxed for 2 h. Then the mixture was concentrated. The residue was diluted with EtOAc (50 mL). The mixture was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was dried to afford methyl 3-(4-(chloromethyl)phenoxy)benzoate as a colorless oil (620 mg, 86%).



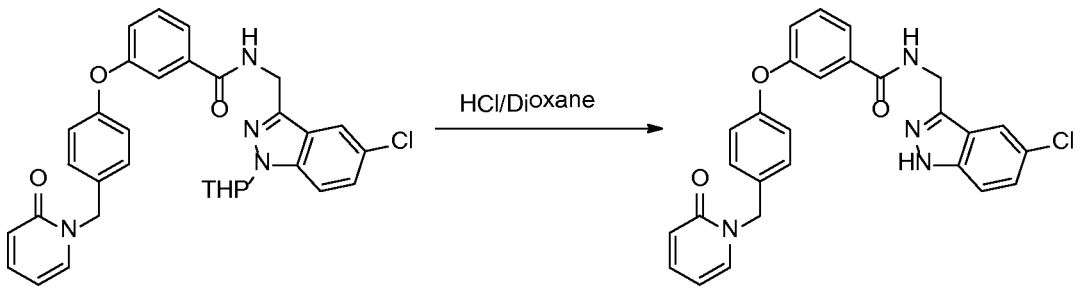
A mixture of methyl 3-(4-(chloromethyl)phenoxy)benzoate (300 mg, 1.08 mmol, 1.0 eq), pyridin-2(1H)-one (124 mg, 1.30 mmol, 1.2 eq) and K_2CO_3 (447 mg, 3.24 mmol, 3.0 eq) in CH_3CN (10 mL) was stirred at 80 °C overnight. After cooled to rt, the mixture was filtered. The filtrate was concentrated. The residue was purified on silica gel column (PE/EtOAc = 1/1) to afford methyl 3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzoate as a yellow oil (300 mg, 83%).



To a solution of methyl 3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzoate (300 mg, 0.9 mmol, 1.0 eq) in MeOH (5 mL) and H_2O (5 mL) was added NaOH (107 mg, 2.7 mmol, 3.0 eq). The mixture was stirred at rt for 1 h. The organic solvents were evaporated. To the residue was added conc. HCl till pH 2. The precipitate was collected and dried to afford 3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzoic acid as a white solid (250 mg, 86%).

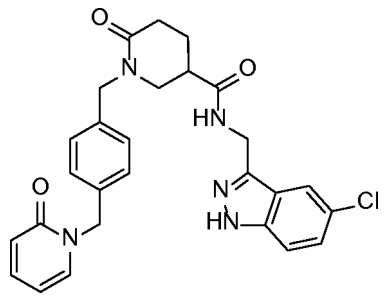


A mixture of 3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzoic acid (250 mg, 0.78 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (248 mg, 0.93 mmol, 1.2 eq), HATU (593 mg, 1.56 mmol, 2.0 eq) and DIEA (302 mg, 2.34 mmol, 3.0 eq) in DMF (10 mL) was stirred at 60 °C overnight. The mixture was poured into water (50 mL). The precipitate was collected and dried to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzamide as a brown solid (420 mg, 95%).

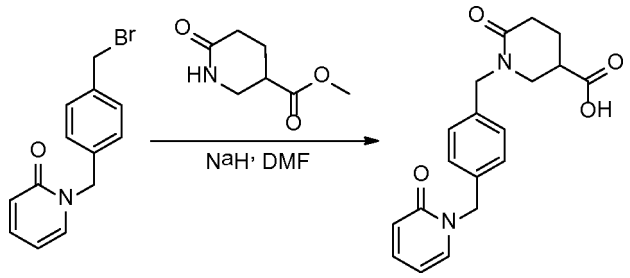


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzamide (420 mg, 0.74 mmol, 1.0 eq) in MeOH (1 mL) and HCl/dioxane (5 N, 5 mL) was stirred at rt for 2 h. Then the mixture was concentrated. The residue was recrystallized with MeOH/EtOAc to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzamide as a white solid (20.6 mg, 6%). LRMS ($M+H^+$) m/z calculated 485.1, found 485.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.06 (s, 1H), 9.17 (t, 1H), 7.89 (d, 1H), 7.82-7.80 (m, 1H), 7.66 (d, 1H), 7.50-7.30 (m, 7H), 7.17 (s, 1H), 7.01 (d, 2H) , 6.41 (d, 1H), 6.24 (t, 1H), 5.07 (s, 2H), 4.75 (d, 2H).

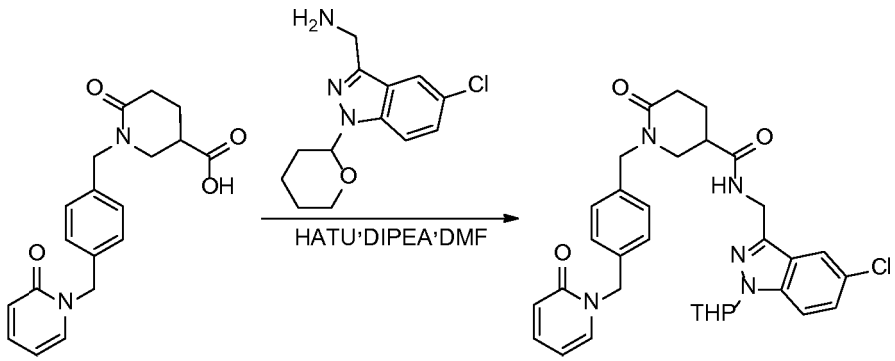
Example 25: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide



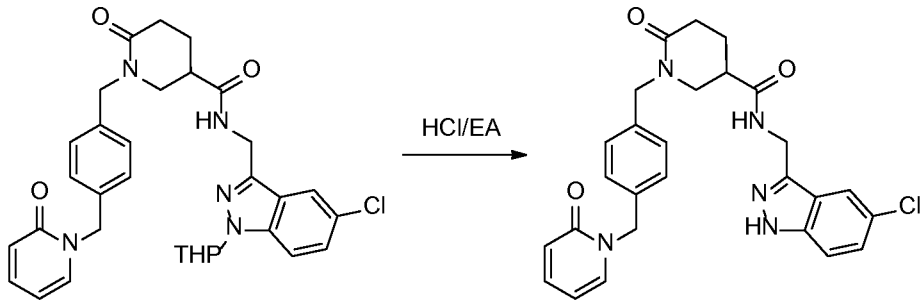
N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide



To a solution of methyl 6-oxopiperidine-3-carboxylate (113 mg, 0.72 mmol, 1.0 eq) in DMF (2 mL) was added NaH (86 mg, 2.16 mmol, 3.0 eq) at 0 °C under N_2. The suspension was stirred at 0 °C for 15 min, then 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (200 mg, 0.72 mmol, 1.0 eq) was added into the mixture. The mixture was stirred at rt for 2 h. The reaction mixture was poured into ice-water (5 mL), acidified with 1 N HCl to pH 2-3, and concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford 6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxylic acid as a yellow solid (80 mg, 33%).

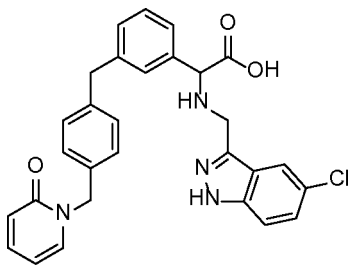


To a solution of 6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxylic acid (80 mg, 0.24 mmol, 1.0 eq) in DMF (3 mL) were added DIPEA (93 mg, 0.72 mmol, 3.0 eq) and HATU (109 mg, 0.29 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min. (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (69 mg, 0.26 mmol, 1.1 eq) was added into the mixture. The mixture was stirred at rt overnight under N_2. The mixture was poured into water (10 mL), extracted with EA (10 mL ×3); the combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide as a yellow solid (120 mg, 85%).

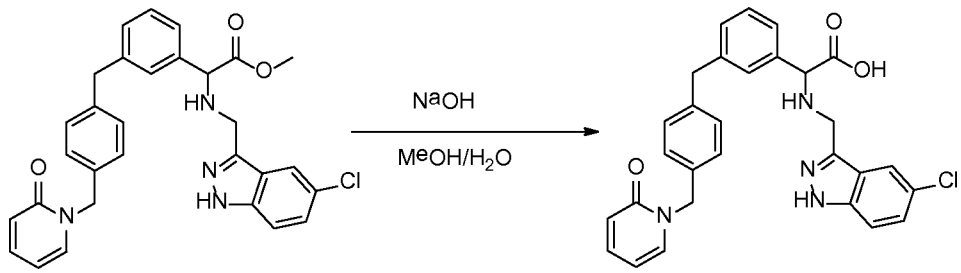


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide (120 mg, 0.2 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/EA (2 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL), neutralized with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide as a white solid (70 mg, 69%). LRMS ($M+H^+$) m/z caculated 504.1, found 504.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.04 (brs, 1 H), 8.59 (t, 1 H), 7.80-7.75 (m, 2 H), 7.52 (d, 1 H), 7.42 (t-d, 1 H), 7.33 (d, 1 H), 7.28-7.12 (m, 4 H), 6.40 (d, 1 H), 6.22 (t, 1 H), 5.06 (s, 2 H), 4.60-4.30 (m, 4 H), 3.28-3.15 (m, 2 H), 2.80-2.60 (m, 1 H), 2.40-2.20 (m, 2 H), 2.00-1.80 (m, 2 H).

Example 26: Preparation of 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)phenyl)acetic acid



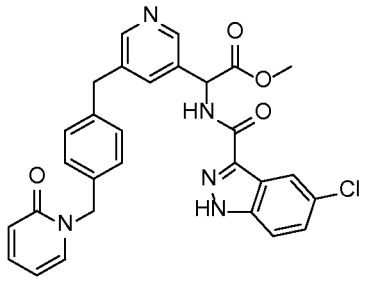
2-(((5-chloro-1*H*-indazol-3-yl)methyl)amino)-2-(3-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)phenyl)acetic acid



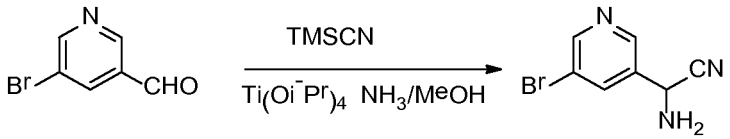
To a solution of methyl 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)phenyl)acetate (180 mg, 0.31 mmol, 1.0 eq) in MeOH (10 mL) and H_2O (5 mL) was added NaOH (128 mg, 3.1 mmol, 10.0 eq). The mixture was stirred at 70 °C for 3 h. The organic solvents were evaporated. To the residue was added conc HCl till pH 3. The precipitation formed was filtered and dried to afford 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(3-(4-((2-oxopyridin-1(2H)-

yl)methyl)benzyl)phenyl)acetic acid as a white solid (62 mg, 38%). LRMS ($M+H^+$) m/z calculated 513.2, found 513.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.13 (s, 1H), 7.91 (s, 1H), 7.74 (d, 1H), 7.53 (m, 1H), 7.41-7.32 (m, 2H), 7.24-7.10 (m, 8H), 7.08 (d, 1H), 6.38 (d, 1H) , 6.20 (t, 1H), 5.02 (s, 2H), 4.23 (s, 1H), 4.04 (d, 2H), 3.87 (s, 2H).

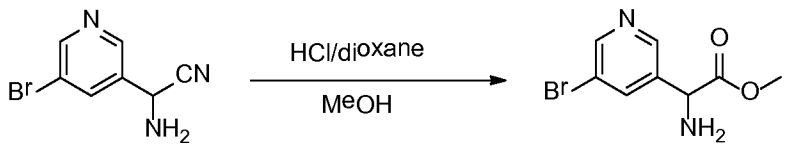
Example 27: Preparation of methyl 2-(5-chloro-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate



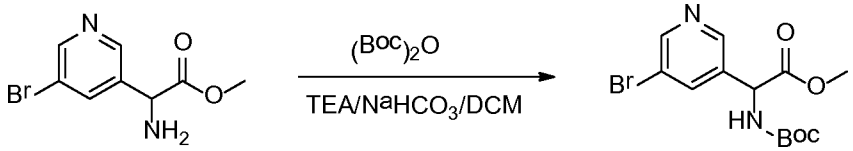
methyl 2-(5-chloro-1*H*-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)pyridin-3-yl)acetate



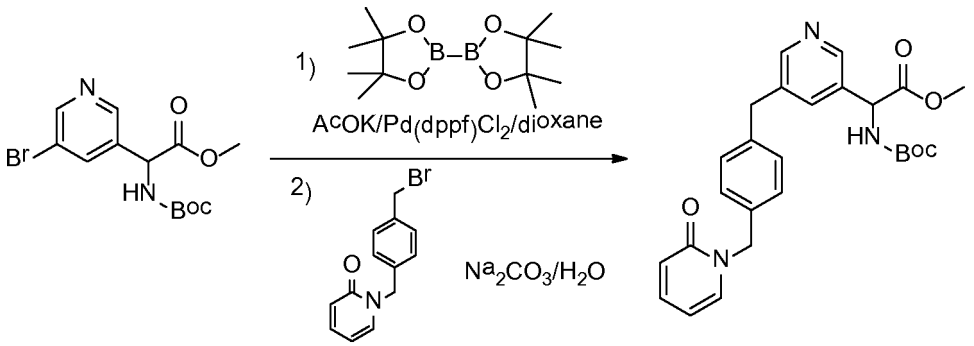
To a stirred solution of 5-bromonicotinaldehyde (4.5 g, 24 mmol, 1.0 eq) in ammonia solution (60 ml, 5 M solution in methanol) was added tetraisopropyl orthotitanate (8.2 g, 29 mmol, 1.2 eq) and the resulting mixture was stirred at r.t. for 2 h. Trimethylsilylcyanide (2.4 g, 24 mmol, 1.0 eq) was then added dropwise and stirring continued at rt for 22 h. The reaction mixture was poured into ice-water (300 mL). After stirring, the resulting mixture was filtered through celite, washing with ethyl acetate (80 mLx3). The filtrate was concentrated in vacuo and the residue was taken up in ethyl acetate and washed sequentially with distilled water and with saturated brine. The organic phase was then dried over sodium sulphate and concentrated in vacuo to give an oil, which was further purified by flash chromatography to afford 2-amino-2-(5-bromopyridin-3-yl)acetonitrile (1.3 g, 25%) as a yellow solid.



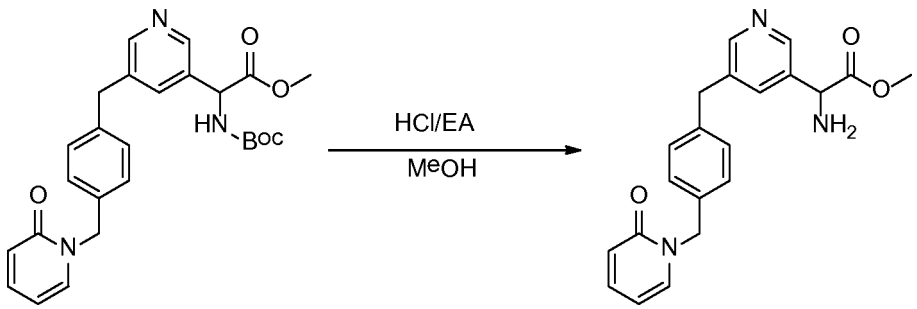
To a solution of 2-amino-2-(5-bromopyridin-3-yl)acetonitrile in 10 mL of methanol was added drop wise HCl/dioxane (5 N, 5 mL). The mixture was stirred at rt overnight and then heated to reflux for 3 h. After cooling to rt, the mixture was concentrated under reduced pressure, the residue was poured into saturated $NaHCO_3$ (60 mL), extracted with EA (50 mLx 3) and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give methyl 2-amino-2-(5-bromopyridin-3-yl)acetate (1.0 g, 66%) as a yellow oil.



2-Amino-2-(5-bromopyridin-3-yl)acetate (1.0 g, 4.0 mmol, 1.0 eq) was diluted with dichloromethane (60 mL) and slowly added with $NaHCO_3$ (685 mg, 8.1 mmol, 2.0 eq), triethylamine (1.0 mL, 8.1 mmol, 2.0 eq), and di- *tert*-butyl dicarbonate (1.0 g, 4.8 mmol, 1.2 eq) at rt in sequence. The reaction solution was stirred for 2 h at the same temperature, and slowly added with a saturated aqueous solution of ammonium chloride (100 mL). The aqueous layer was extracted twice with ethyl acetate. The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel column (PE/EA = 30/1 to 3/1) to afford methyl 2-(5-bromopyridin-3-yl)-2-((*tert*-butoxycarbonyl)amino)acetate (759 mg, 54%).

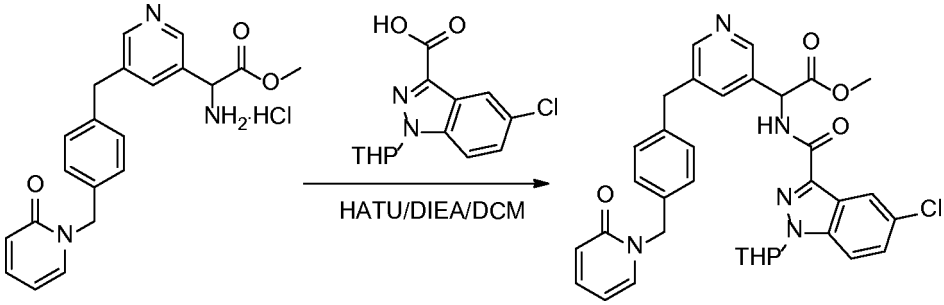


To a suspension of methyl 2-(5-bromopyridin-3-yl)-2-((*tert*-butoxycarbonyl)amino)acetate (710 mg, 2.0 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (523 mg, 2.0 mmol, 1.0 eq) and AcOK (605 mg, 6.1 mmol, 3.0 eq) in dioxane (40 mL) was added $Pd(dppf)Cl_2$ (75 mg, 0.1 mmol, 0.05 eq). The mixture was heated to 85 °C under N_2 overnight. After cooled to rt, 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (480 mg, 2.0 mmol, 1.0 eq), and a solution of Na_2CO_3 (654 mg, 6.1 mmol, 3.0 eq) in water (6 mL) were added, followed by $Pd(dppf)Cl_2$ (75 mg, 0.1 mmol, 0.05 eq). The mixture was then heated to 95 °C for a further 2 h and allowed to cool. After removal of the solvent, the residue was poured into water (60 mL), extracted with EA (3x60 mL), the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an oil, which was further purified by chromatography on silica gel column (PE/EA = 2/1, then DCM/MeOH = 10/1) to afford methyl 2-((tert-butoxycarbonyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate (443 mg, 46%) as a white solid.

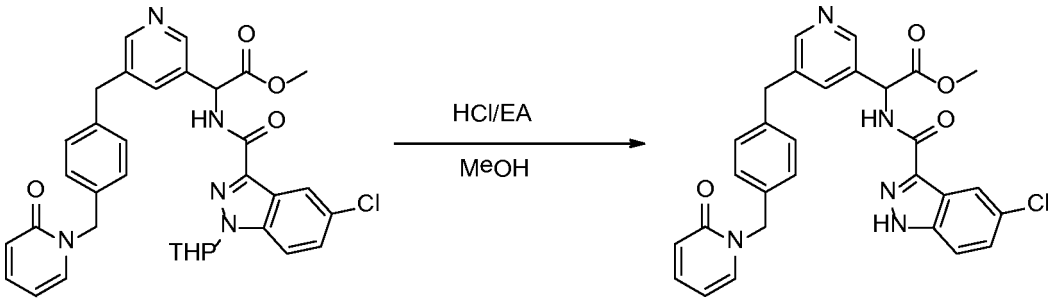


A solution of methyl 2-((*tert*-butoxycarbonyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate (440 mg, 0.95 mmol, 1.0 eq) in MeOH (5 mL) and HCl/EA (3 N, 3 mL) was stirred at rt for 20 h.

Then the mixture was concentrated to afford methyl 2-amino-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate HCl salt as a white solid (397 mg, 95%).

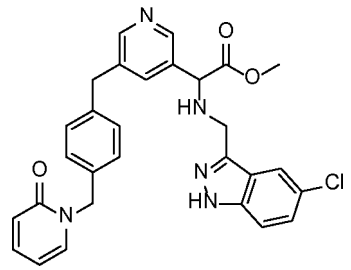


A mixture of 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxylic acid (130 mg, 0.46 mmol, 1.0 eq), methyl 2-amino-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate HCl salt (202 mg, 0.46 mmol, 1.0 eq), HATU (176 mg, 0.46 mmol, 1.0 eq) and DIEA (1 mL) in DCM (30 mL) was stirred at rt for 20 h. The mixture was diluted with DCM (30 mL), washed with saturated $NaHCO_3$ (20 mL), and the brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was then further purified by flash chromatography (MeCN/H_2O = 25%- 95%) to afford methyl 2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate as a white solid (150 mg, 51%).

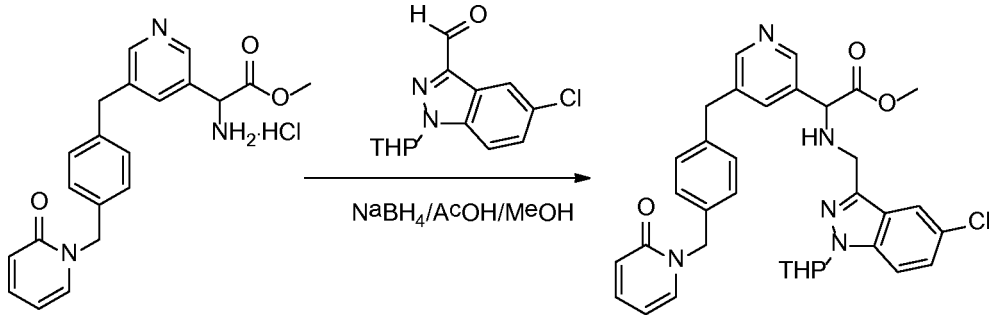


A solution of methyl 2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate (50 mg, 0.079 mmol, 1.0 eq) in MeOH (3 mL) and HCl/EA (3 N, 2 mL) was stirred at 40 °C for 5 h. Then the mixture was concentrated. The residue was purified by flash chromatography (MeCN/H_2O = 1/2 to 5/1) to afford methyl 2-(5-chloro-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate as a white solid (26 mg, 60%). LRMS ($M+H^+$) m/z calculated 542.1, found 542.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.93 (s, 1H), 9.26 (d, 1H), 8.52 (d, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.76-7.68 (m, 3H), 7.46-7.37 (m, 2H), 7.23-7.18 (m, 4H), 6.38 (d, 1H), 6.21 (m, 1H), 5.80 (d, 2H), 5.02 (s, 2H), 3.94 (s, 2H), 3.65 (s, 2H).

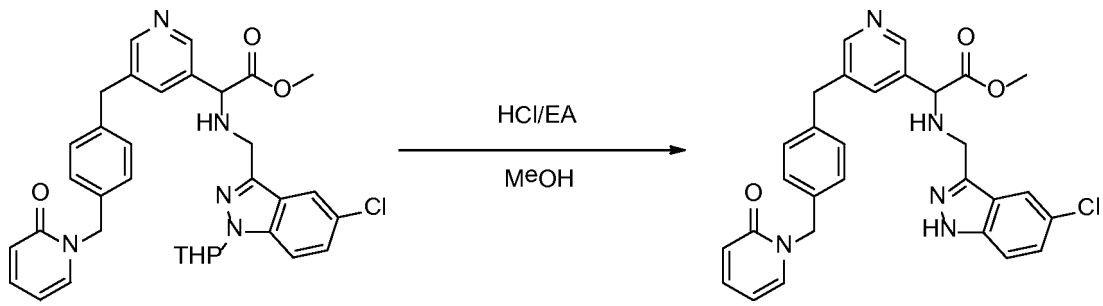
Example 28: Preparation of methyl 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate



methyl 2-(((5-chloro-1*H*-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)pyridin-3-yl)acetate

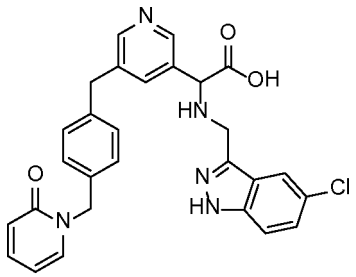


A mixture of 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carbaldehyde (73 mg, 0.27 mmol, 1.0 eq), methyl 2-amino-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate HCl salt (100 mg, 0.27 mmol, 1.0 eq) and AcOH (5 drops) in MeOH (3 mL) was stirred at rt for 1 h. $NaBH_4$ (209 mg, 5.5 mmol, 20 eq) was then added portion wise. The mixture was stirred at rt for a further 1 h and then quenched with water (2 mL). After workup, it was purified by flash chromatography ($MeCN/H_2O$ = 1/3 to 10/1) to afford methyl 2-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate (42 mg, 25%) as a white solid.

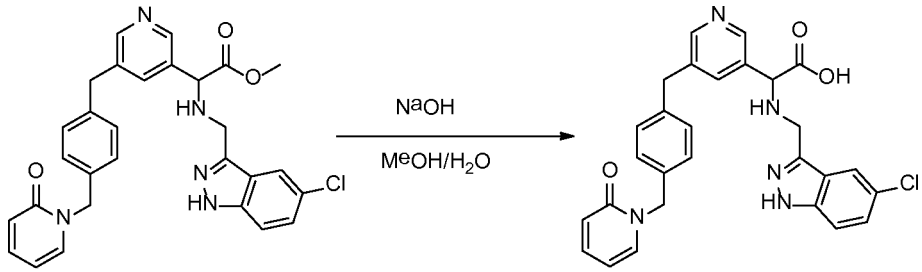


A solution of methyl 2-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate (40 mg, 0.065 mmol, 1.0 eq) in MeOH (2 mL) and HCl/EA (3 N, 3 mL) was stirred at 50 °C for 2 h. Then the mixture was concentrated. The residue was purified by flash chromatography ($MeCN/H_2O$ = 1/5 to 3/2) to afford methyl 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate as a white solid (31 mg, 89%). LRMS ($M+H^+$) m/z calculated 528.2, found 528.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 12.98 (s, 1H), 8.36 (m, 2H), 7.89 (s, 1H), 7.75-7.72 (m, 1H), 7.61 (s, 1H), 7.52-7.49 (m, 1H), 7.42-7.30 (m, 2H), 7.20-7.16 (m, 4H), 6.40-6.37 (m, 1H), 6.22-6.18 (m, 1H), 5.04 (d, 2H), 4.49-4.45 (m, 1H), 3.99-3.91 (m, 4H), 3.56 (s, 3H), 3.28-3.23 (m, 1H).

Example 29: Preparation of 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid

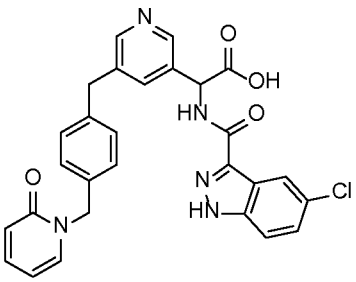


2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid

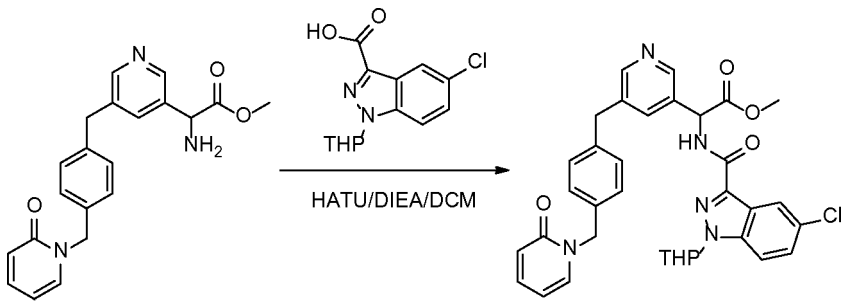


To a solution of methyl 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate (23 mg, 0.037 mmol, 1.0 eq) in MeOH (3 mL) and H_2O (2 mL) was added NaOH (15 mg, 0.38 mmol, 10.0 eq). The mixture was stirred at 70 °C for 2 h. The organic solvents were evaporated. To the residue was added conc. HCl till pH 3 and then evaporated under reduced pressure to give a solid, which was further purified by flash chromatography (MeCN/H_2O = 1/9 to 3/2) to afford 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid as a white solid (19 mg, 85%). LRMS ($M+H^+$) m/z calculated 514.1, found 514.1. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.12 (s, 1H), 8.35 (d, 2H), 7.93 (s, 1H), 7.74 (d, 1H), 7.63 (d, 1H), 7.53 (q, 1H), 7.42-7.32 (m, 2H), 7.19-7.16 (m, 4H), 6.39 (m, 1H), 6.20 (t, 1H), 4.35 (s, 1H), 4.10 (d, 2H), 3.88 (s, 2H).

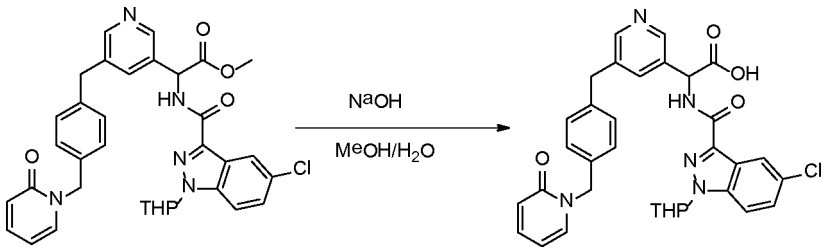
Example 30: Preparation of 2-(5-chloro-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid



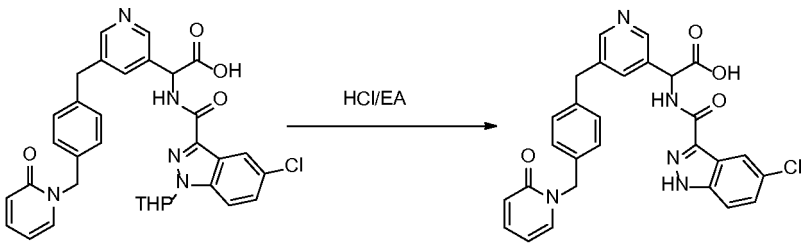
2-(5-chloro-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid



A mixture of methyl 2-amino-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate (202 mg, 0.46 mmol, 1.0 eq), 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxylic acid (130 mg, 0.46 mmol, 1.0 eq), HATU (176 mg, 0.46 mmol, 1.0 eq) and DIEA (1 mL) in DCM (30 mL) was stirred at rt for 20 h. Then the mixture was diluted with DCM (30 mL), washed with saturated $NaHCO_3$ aqueous (20 mL) and then brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an oil, which was further purified by flash chromatography (MeCN/H_2O = 1/2 to 19/1) to afford methyl 2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate as a white solid (150 mg, 51%).

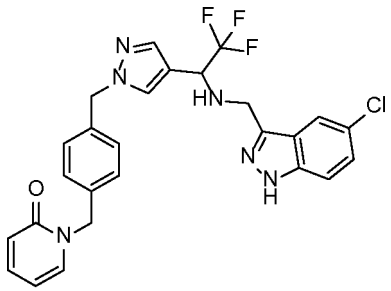


To a solution of methyl 2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate (100 mg, 0.15 mmol, 1.0 eq) in MeOH (10 mL) and H_2O (5 mL) was added NaOH (64 mg, 1.5 mmol, 10.0 eq). The mixture was then stirred at rt for 20 h. The organic solvents were evaporated. To the residue was added conc. HCl till pH 3. The mixture was then evaporated under reduced pressure to give a solid, which was further purified by flash chromatography (MeCN/H_2O = 1/2 to 19/1) to afford 2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid as a white solid (81 mg, 83%).

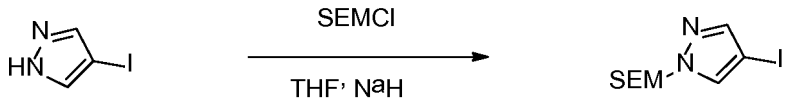


A solution of 2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid (40 mg, 0.065 mmol, 1.0 eq) in HCl/EA (3 N, 5 mL) was stirred at rt for 20 h. Then the mixture was concentrated. The residue was purified by flash chromatography (MeCN/H_2O = 1/9 to 3/2) to afford 2-(5-chloro-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid as a white solid (9 mg, 26%). LRMS ($M+H^+$) m/z calculated 528.1, found 528.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.13 (s, 1H), 7.91 (s, 1H), 7.74 (d, 1H), 7.53 (m, 1H), 7.41-7.32 (m, 2H), 7.24-7.10 (m, 8H), 7.08 (d, 1H), 6.38 (d, 1H), 6.20 (t, 1H), 5.02 (s, 2H), 4.23 (s, 1H), 4.04 (d, 2H), 3.87 (s, 2H).

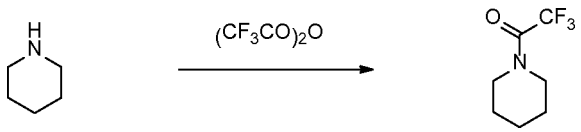
Example 31: Preparation of 1-(4-((4-(1-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one



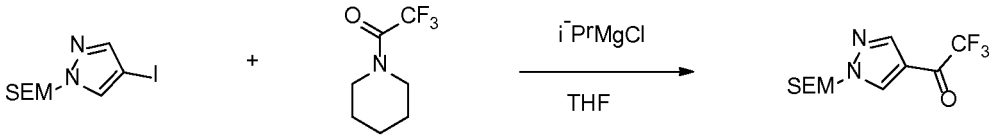
1-(4-((4-(1-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one



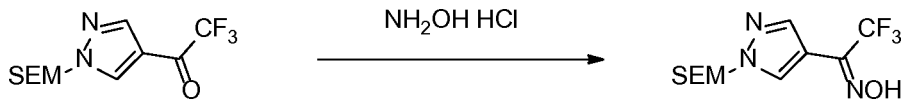
4-iodo-1H-pyrazole (5.03 g, 25.92 mmol, 1.0 eq) was dissolved in dry THF (40 mL), NaH (4.16 g, 60%, 4.0 eq) was added in portions. T he resulting mixture was stirred at rt for 30 min. To this mixture was added (2-(chloromethoxy)ethyl)trimethylsilane (6.47 g, 38.89 mmol, 1.5 eq) dropwise. The reaction was stirred at ambient temperature for 2 h, then poured into saturated aqueous NH_4Cl. The mixture was extracted with EA, washed with water, brine, dried over anhydrous sodium sulfate, and purified on silica gel column to afford desired 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (7.5 g, 89%).



To the solution of triethylamine (14.6 mL, 105 mmol, 1.0 eq), piperidine (12.6 g, 126 mmol, 1.2 eq) in DCM (40 mL) was added trifluoroacetic anhydride (14.8 mL, 105 mmol, 1.0 eq) at 0 °C over 30 min. The resulted mixture was stirred at 0 °C for 30 min then at rt for 1 h, and then quenched with water. The DCM layer was washed with 1N HCl, brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford 2,2,2-trifluoro-1-(piperidin-1-yl)ethanone as yellow oil (13.2 g, 70%).

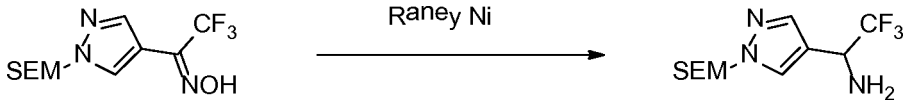


To a solution of 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (4.0 g, 12.34 mmol, 1.0 eq) in dry THF (100 mL) at 0 °C was added iPrMgBr (1.0 M, 18.5 mL, 18.5 mmol, 1.5 eq) quickly. The mixture was stirred for 30 min, then cooled to -78 °C. a solution of 2,2,2-trifluoro-1-(piperidin-1-yl)ethanone (4.46 g, 24.68 mmol, 2.0 eq, dissolved in 20 mL of THF) was added quickly. The reaction mixture was stirred for 1 h, quenched with saturated aqueous NH_4Cl, extracted with EA. The extracts were washed with water, brine, dried over Na_2SO_4, filtered and purified on silica gel column (PE/EA = 10/1) to afford 2,2,2-trifluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)ethanone as colorless oil (5.2 g, crude).

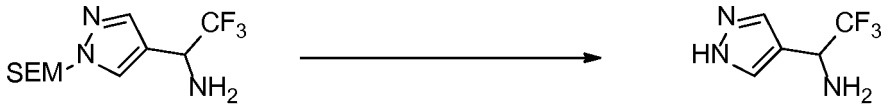


2,2,2-trifluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)ethanone (5.23 g, crude, obtained above) was dissolved in pyridine (45 mL) and EtOH (15 mL). $H_2NOH.HCl$ (1.35 g, 19.46 mmol) was added

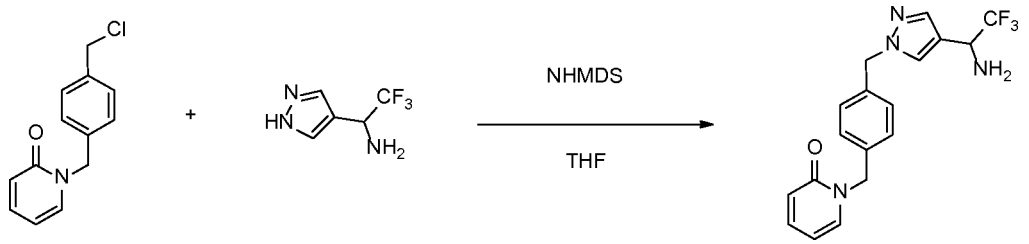
to this solution. The reaction mixture was stirred at 60 °C for 3 h, and then concentrated. The residue wasdissolved in EA (100 mL), washed with 1 N HCl (100 m L X2), brine, dried over anhydrous sodium sulfate, and purified via flash chromatography to afford 2,2,2-trifluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)ethanone oxime as colorless oil (3.4 g, 89%).



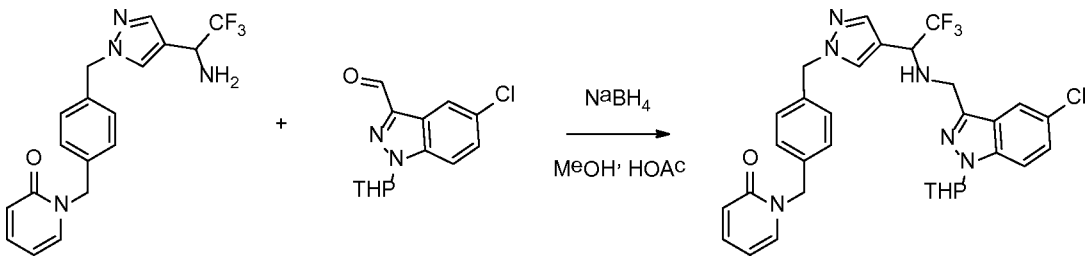
2,2,2-trifluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)ethanone oxime (3.4 g, 11.0 mmol, 1.0 eq) and Raney Ni were mixed in MeOH (30 mL) and hydrogenated overnight, filtered through celite, concentrated, purified via flash chromatography to afford 2,2,2-trifluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)ethanamine (1.2 g, 80% purity) which was used without further purification.



The solution of 2,2,2-trifluoro-1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)ethanamine (1.2 g, 4.0 mmol, 1.0 eq) in methanol (3 mL) was treated with TFA (1 mL) and stirred at 30 °C for 30 min. The mixture was concentrated, basified with saturated aqueous $NaHCO_3$, and concentrated. The residue was purified via flash chromatography to afford 2,2,2-trifluoro-1-(1H-pyrazol-4-yl)ethanamine as a white solid (400 mg, 59%).

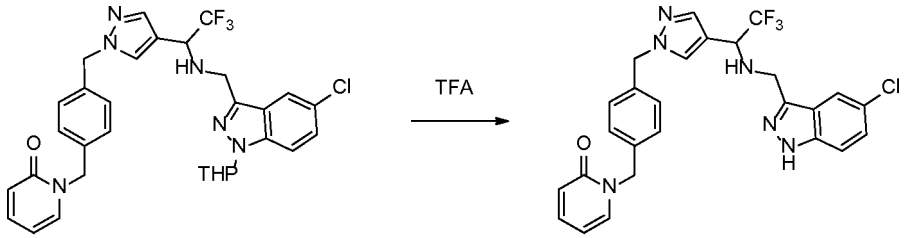


To a solution of 2,2,2-trifluoro-1-(1H-pyrazol-4-yl)ethanamine (200 mg, 1.2 mmol, 1.0 eq) in dry THF (10 mL) was added NaHMDS (2.0 M, 0.575 mL, 1.15 mmol, 0.95 eq) at -10 °C. The mixture was stirred at this temperature for 30 min, and then 1-(4-(chloromethyl)benzyl)pyridin-2(1H)-one (282 mg, 1.21 mmol, 1.0 eq) was added. Tthe cool bath was removed and the reaction mixture was stirred at 60 °C overnight, quenched with saturated aqueous NH_4Cl, concentrated. The residue was purified via flash chromatography to afford 1-(4-((4-(1-amino-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one as a white solid (230 mg, 52%).



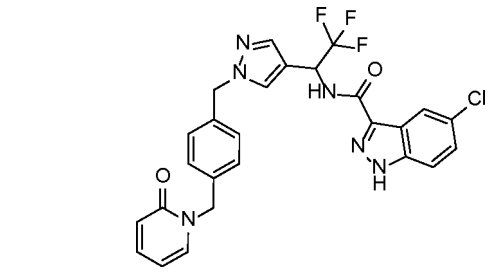
To the mixture of 1-(4-((4-(1-amino-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one (110 mg, 0.317 mmol, 1.0 eq) in MeOH (2 mL) was added 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carbaldehyde (84 mg, 0.317 mmol, 1.0 eq) followed by two drops of HOAc.The mixture was

stirred for 1 h, and $NaBH_4$ (48 mg, 1.26 mmol, 4.0 eq) was added in portions till the reaction was complete. The mixture was concentrated, and the residue was dissolved in DCM, washed with water, brine, dried over anhydrous sodium sulfate, and purified via flash chromatography to afford 1-(4-((4-(1-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one as a white solid (110 mg, 56%).

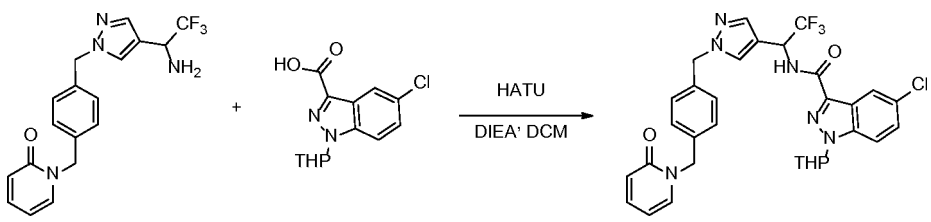


1-(4-((4-(1-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one (110 mg, 0.18 mmol, 1.0 eq) was stirred in TFA (1.5 mL) for 1 h, and then concentrated. The residue was neutralized with 1 N NaOH, concentrated, and triturated in 20% MeOH in DCM. The filtrate was concentrated and purified via reverse flash chromatography to afford 1-(4-((4-(1-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one as a white solid (45 mg, 52%). LRMS $(M+H)^+$ m/z calculated 527.1, found 527.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.96 (s, 1 H), 7.90 (s, 1 H), 7.85 (s, 1 H), 7.77 (d, 1 H), 7.54-7.46 (m, 2 H), 7.41 (dt, 1 H), 7.32 (d, 1 H), 7.25 (d, 2 H), 7.16 (d, 2 H), 6.40 (d, 1 H), 6.22 (t, 1 H), 5.28 (s, 2 H), 5.06 (s, 2 H), 4.39 - 4.28 (m, 1 H), 4.08 (dd, 1 H), 3.98 (dd, 1 H), 3.18-3.08 (m, 1 H).

Example 32: Preparation of 5-chloro-N-(2,2,2-trifluoro-1-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazol-4-yl)ethyl)-1H-indazole-3-carboxamide

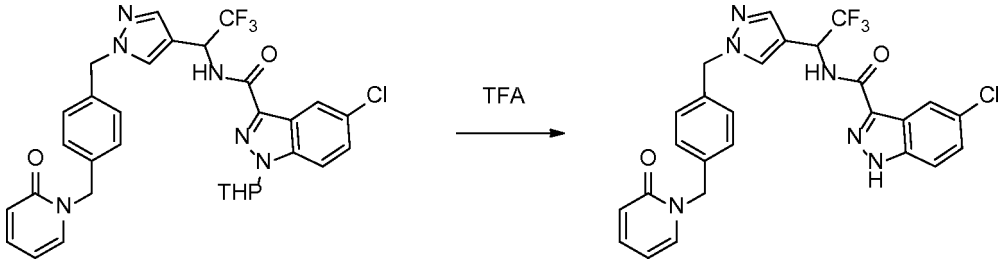


5-chloro-N-(2,2,2-trifluoro-1-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazol-4-yl)ethyl)-1H-indazole-3-carboxamide



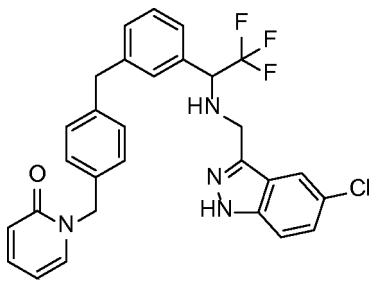
The mixture of 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxylic acid (124 mg, 0.44 mmol, 1.0 eq), HATU (251 mg, 0.66 mmol, 1.5 eq) and DIEA (0.2 mL) in DCM (10 mL) was stirred for 10 min and then 1-(4-((4-(1-amino-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one (160 mg, 0.44 mmol, 1.0 eq) was added. The reaction mixture was stirred for 1.5 h, quenched with saturated aqueous sodium

bicarbonate. The organic layer was washed with water, brine, and purified via flash chromatography to afford 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-N-(2,2,2-trifluoro-1-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazol-4-yl)ethyl)-1H-indazole-3-carboxamide as a white solid (200 mg, 72%).

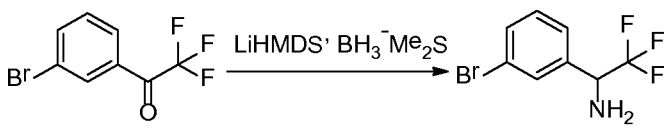


The mixture of 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-N-(2,2,2-trifluoro-1-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazol-4-yl)ethyl)-1H-indazole-3-carboxamide (200 mg, 0.32 mmol, 1.0 eq) in trifluoroacetic acid was stirred for 1 h, then concentrated and added with saturated aqueous sodium carbonate and DCM. After extraction, the organic phase was concentrated and purified via reverse flash chromatography to afford 5-chloro-N-(2,2,2-trifluoro-1-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazol-4-yl)ethyl)-1H-indazole-3-carboxamide as a white solid (80 mg, 46%). LRMS $(M+H)^+$ m/z calculated 460.1, found 460.1. ^{1}H NMR (DMSO-d6, 400 MHz) δ (ppm) 13.96 (s, 1 H), 9.43 (d, 1 H), 8.10 (s, 2 H), 7.75 (dd, 2 H), 7.70 (d, 1 H), 7.47 (dd, 1 H), 7.40 (dt, 1 H), 7.23 (m, 4 H), 6.39 (d, 1 H), 6.20 (dt, 1 H), 6.06 (t, 1 H), 5.30 (s, 2 H), 5.05 (s, 2 H).

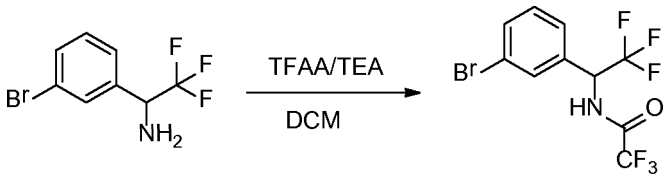
Example 33: Preparation of 1-(4-(3-(1-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)benzyl)benzyl)pyridin-2(1H)-one



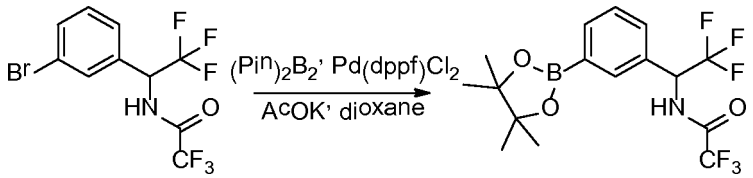
1-(4-(3-(1-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)benzyl)benzyl)pyridin-2(1H)-one



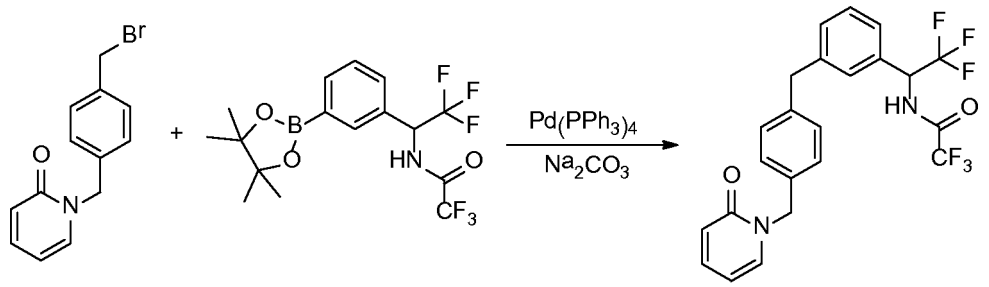
To a solution of 1-(3-bromophenyl)-2,2,2-trifluoroethanone (1.01 g, 4.0 mmol, 1 eq) in toluene (20 mL) was added LiHMDS (1 M in THF, 4.4 mL, 1.1 eq) dropwise at rt and the mixture was stirred at rt for 15 min. Then $BH_3 \cdot Me_2S$ (2 M, 4 mL, 2.0 eq) was added. The mixture was stirred at rt for 20 min. The mixture was diluted with water, extracted with EA (3x20 mL). The combined organic layers were concentrated, and purified by flash chromatography (PE/EA = 10/1-5/1) to afford 1-(3-bromophenyl)-2,2,2-trifluoroethanamine as a white solid (500 mg, 50%).



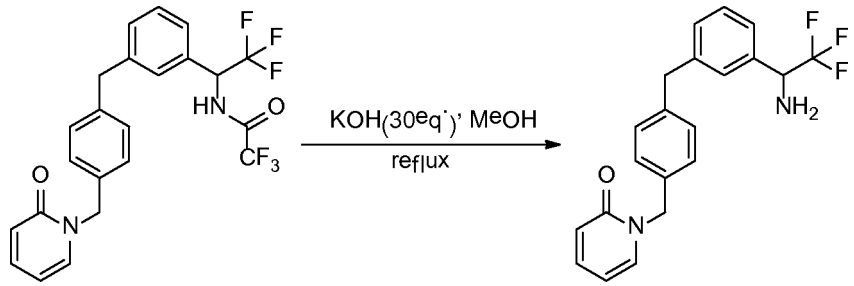
To a solution of 1-(3-bromophenyl)-2,2,2-trifluoroethanamine (506 mg, 2.0 mmol, 1 eq), and TEA (606 mg, 6.0 mmol, 3 eq) in DCM (10 mL) was added TFAA (462 mg, 2.2 mmol) in 3 mL of DCM at 0 °C under N_2. The reaction mixture was stirred at rt for 2 h, diluted with water, and extracted with EA (3x20 mL). The combined organic layers were washed with brine, concentrated, and purified on silica gel column (PE/EA = 20/1-10/1) to afford N-(1-(3-bromophenyl)-2,2,2-trifluoroethyl)-2,2,2-trifluoroacetamide as a colorless oil (600 mg, 86%).



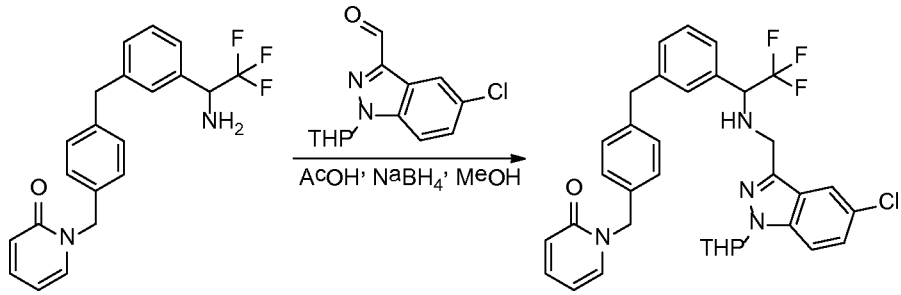
A mixture of N-(1-(3-bromophenyl)-2,2,2-trifluoroethyl)-2,2,2-trifluoroacetamide (140 mg, 0.47 mmol, 1.0 eq), $(Pin)_2B_2$ (140 mg, 0.47 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (140 mg, 0.47 mmol, 1.0 eq) and AcOK (140 mg, 0.47 mmol, 1.0 eq) in dioxane (8 mL) was stirred at 80 °C under N_2 atmosphere overnight. The mixture was diluted with water, extracted with EA (3x20 mL). The combined organic layers were washed with brine, and concentrated. The residue was purified by prep-TLC to afford 2,2,2-trifluoro-N-(2,2,2-trifluoro-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)acetamide as a white solid (14 mg, 10%).



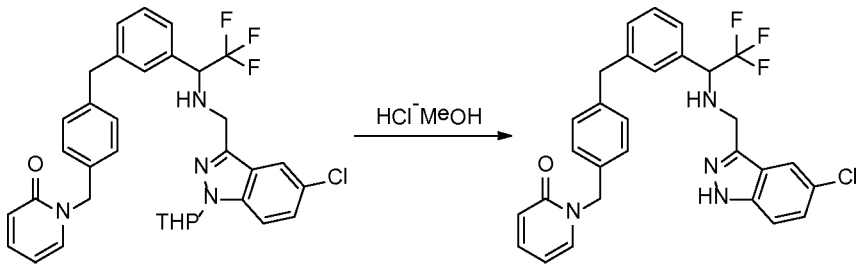
A mixture of 2,2,2-trifluoro-N-(2,2,2-trifluoro-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)acetamide (200 mg, 0.50 mmol, 1.0 eq) and 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (140 mg, 0.50 mmol, 1.0 eq), $Pd(PPh_3)_4$ (58 mg, 0.050 mmol, 0.1 eq) and Na_2CO_3 (159 mg, 1.50 mmol, 3.0 eq) in dioxane-H_2O (7 mL / 1 mL) was stirred at 80 °C under N_2 atmosphere overnight. Then the mixture was filtered and the filtrate concentrated. The residue was diluted with water, extracted with EA (3x20 mL). The combined organic layers were washed with brine, concentrated. The residue was purified by prep-TLC to afford 2,2,2-trifluoro-N-(2,2,2-trifluoro-1-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)phenyl)ethyl)acetamide as a white solid (70 mg, 30%).



To a solution of 2,2,2-trifluoro-N-(2,2,2-trifluoro-1-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)phenyl)ethyl)acetamide (70 mg, 0.15 mmol, 1.0 eq) in MeOH/H_2O (10 mL / 2 mL) was added KOH (252 mg, 0.48 mmol, 30 eq). The mixture was refluxed for 2 h. It was diluted with water, extracted with EA (3x20 mL). The combined organic layers were washed with brine, concentrated, purified by prep-TLC (PE/EA = 1/1) to afford 1-(4-(3-(1-amino-2,2,2-trifluoroethyl)benzyl)benzyl)pyridin-2(1H)-one (40 mg, 72%).



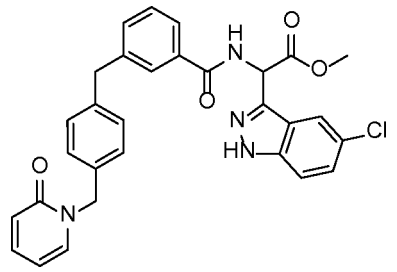
To a solution of 1-(4-(3-(1-amino-2,2,2-trifluoroethyl)benzyl)benzyl)pyridin-2(1H)-one (40 mg, 0.11 mmol, 1 eq) in MeOH (10 mL) was added 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carbaldehyde (29 mg, 0.11 mmol, 1.0 eq), followed with AcOH (13.2 mg, 0.22 mmol, 2 eq). The mixture was stirred at rt for 1 h. $NaBH_4$ (100 eq) was added in 3 portions. The mixture was heated at 50 °C overnight, then diluted with water, extracted with EA (3x20 mL). The combined organic layers were washed with brine, concentrated, purified by prep-TLC (PE/EA = 1/1) to afford 1-(4-(3-(1-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)benzyl)benzyl)pyridin-2(1H)-one as a brown solid (30 mg, 44%).



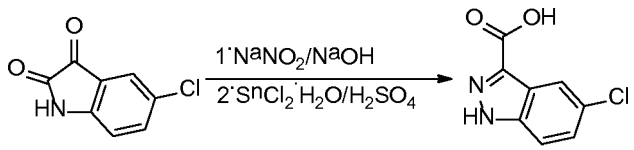
To a stirred suspension of 1-(4-(3-(1-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)benzyl)benzyl)pyridin-2(1H)-one (20 mg, 0.032 mmol, 1.0 eq) in EA (3 mL) was added EA/HCl (4 N, 1 mL). The mixture was stirred at rt for 4 h. After concentration, it was purified by prep-HPLC to afford 1-(4-(3-(1-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)benzyl)benzyl)pyridin-2(1H)-one HCl salt as a white solid (10.0 mg, 51%). LRMS ($M+H^+$) m/z caculated 537.16, found 537.2. ^1H NMR (CD_3OD, 400 MHz) δ 7.91 (d, 1 H), 7.73 (t, 1 H), 7.58 (m, 1 H),

7.48-7.35 (m, 5 H), 7.29-7.24 (dd, 4 H),6.77 (d, 1 H), 6.66(t, 1 H), 5.50 (m, 1 H), 5.26 (s, 2 H), 4.50 (q, 2 H) 3.99 (s, 2 H).

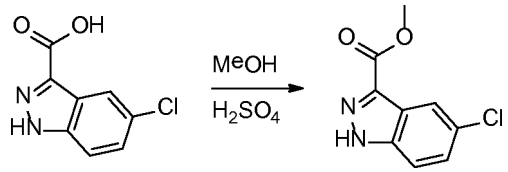
Example 34: Preparation of methyl 2-(5-chloro-1H-indazol-3-yl)-2-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamido)acetate



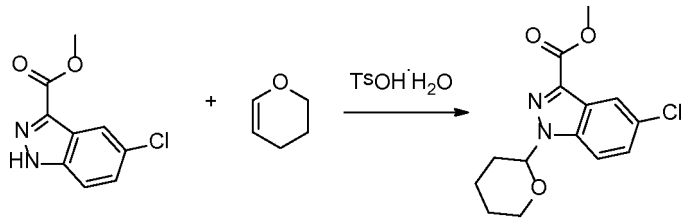
methyl 2-(5-chloro-1*H*-indazol-3-yl)-2-(3-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)benzamido)acetate



To the solution of NaOH (440 mg, 11 mmol, 1.1 eq.) in H_2O (10 mL) was added 5-chloroindoline-2,3-dione (1.81 g, 10 mmol, 1.0 eq). The dark solution was cooled to 0-5 °C. A solution of $NaNO_2$ (828 mg, 12 mmol, 1.2 eq) in H_2O (3 mL) was added. The mixture was added to a solution of conc. H_2SO_4 (2.90 g, 30 mmol, 3.0 eq) in H_2O (30 mL) at 0-5 °C. The mixture was stirred at 0-5 °C for 30 min. A solution of $SnCl_2 \cdot H_2O$ (5.64 g, 25 mmol, 2.5 eq) in conc. HCl (15 mL) was added and the yellow slurry was stirred at rt for 2.5 h. Filtered and the solid was collected to afford 5-chloro-1H-indazole-3-carboxylic acid as a yellow solid (2 g crude, quant).

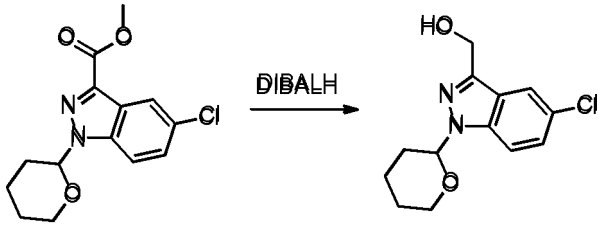


To the solution of 5-chloro-1H-indazole-3-carboxylic acid (2 g, 10 mmol, 1.0 eq.) in MeOH (100 mL) was added conc. H_2SO_4 (3 drops). The mixture was stirred at 75 °C overnight. Filtered and the filtrate was concentrated. The residue was partitioned between saturated $NaHCO_3$ aqueous solution (20 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mLX2). The combined organic extracts were dried over Na_2SO_4 and concentrated to afford methyl 5-chloro-1H-indazole-3-carboxylate as a yellow solid (1.28 g, 61%).

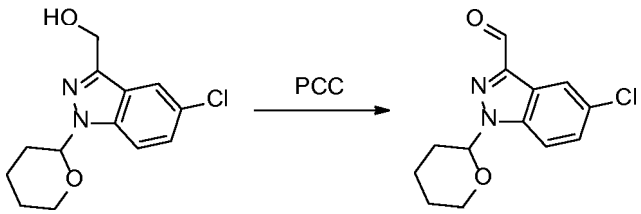


The mixture of methyl 5-chloro-1H-indazole-3-carboxylate (1.28 g, 6.1 mmol, 1.0 eq), 3,4-dihydro-2H-pyran (1.7 mL, 18.7 mmol, 3.0 eq), $TsOH \cdot H_2O$ (120 mg, 0.63 mmol, 0.1 eq) in THF (100 mL) as stirred at 70 °C

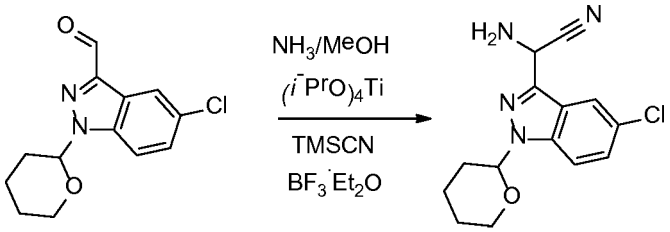
overnight. The mixture was concentrated and the residue was purified on silica column to afford methyl 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxylate as a yellow solid (1.27 g, 73.4 %).



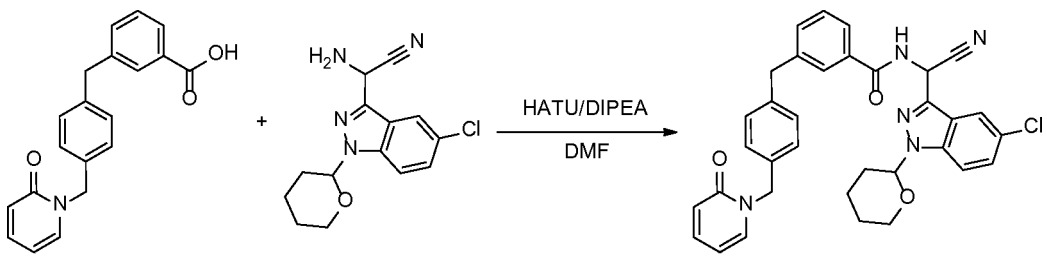
To a solution of methyl 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carboxylate (100 mg, 0.34 mmol, 1.0 eq) was added a solution of DIBAL-H in hexane (1 mol/L, 1 mL, 3.0 eq.) at -70 °C. The mixture was stirred at -78 °C for 1 h and warmed to rt for 2 h. The reaction was quenched with saturated NH_4C1 aqueous solution (10 mL) and extracted with DCM (10 mL X 2). The combined organic extracts were dried over Na_2SO_4 and concentrated to afford (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanol as a white solid (91 mg, quant).



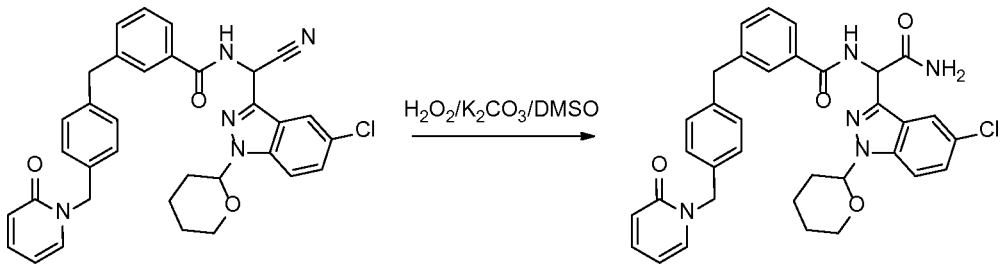
The mixture of (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanol (2.0 g, 7.5 mmol, 1.0 eq.), PCC (4.85 g, 22.5 mmol, 3.0 eq.), and silica gel (100-200 mesh, 3 g) in DCM (60 mL) was stirred at rt for 5 h. Filtered and the filtrate was concentrated. The residue was purified on silica gel column to afford 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carbaldehyde as a light solid (1.18 g, 59.4%).



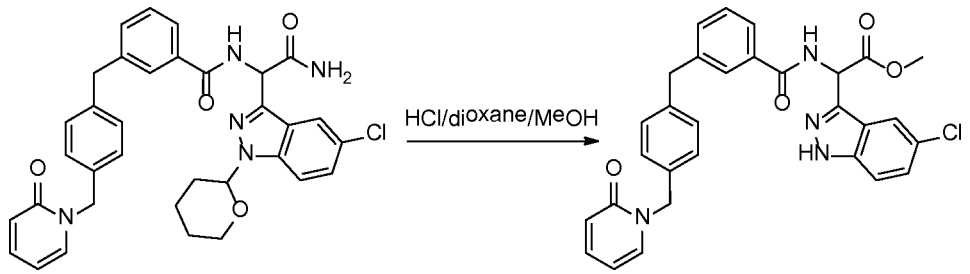
To a solution of 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carbaldehyde (723 mg, 2.73 mmol, 1.0 eq.) in NH_3/MeOH (15 mL) was added (i-PrO)$_4$Ti (0.1 mL). The mixture was stirred at rt for 1 h. $BF_3{\cdot}Et_2O$ (3 drops) was added and followed by addition of TMSCN (1.1 mL, 8.81 mmol, 3.2 eq.). The mixture was stirred at rt overnight and quenched with H_2O (50 mL). Extracted with DCM (50 mL X 3) and the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified on silica gel column to afford 2-amino-2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)acetonitrile as a yellow solid (704 mg, 88.4%).



A mixture of 2-amino-2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)acetonitrile (83 mg, 0.285 mmol, 1 eq), (92 mg , 0.288 mmol, 1.0 eq), HATU (145 mg, 0.38 mmol, 1.3 eq), and DIPEA (0.8 mL) in DMF (3 mL) was stirred at 50 °C overnight. The mixture was purified via prep- MPLC to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)(cyano)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide as a white solid (142 mg, 84%).

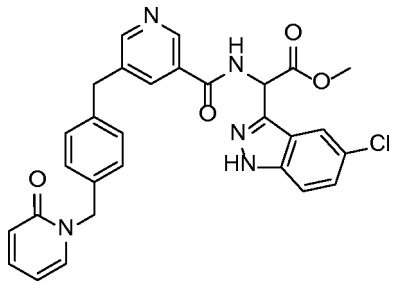


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)(cyano)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide (142 mg, 0.24 mmol, 1.0 eq) in DMSO (3 mL) was added K_2CO_3 (40 mg, 0.29 mmol, 1.2 eq) and H_2O_2 (30% aq., 0.5 mL). The mixture was stirred at rt overnight and purified via prep-MPLC to afford N-(2-amino-1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-2-oxoethyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide as a white solid (75 mg, 51.3%).

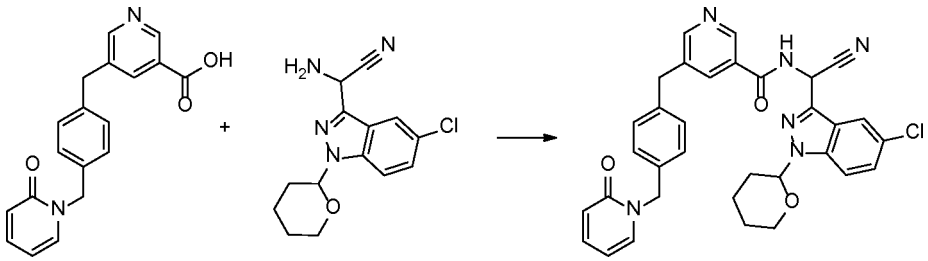


A solution of N-(2-amino-1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-2-oxoethyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide (75 mg, 0.123 mmol, 1 eq) in MeOH (2 mL) and HCl/dioxane (5 N, 2 mL) was stirred at rt overnight, then concentrated. The residue was purified via prep-TLC (DCM/MeOH = 15/1, v/v) to afford methyl 2-(5-chloro-1H-indazol-3-yl)-2-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamido)acetate as a white solid (15 mg, 22.6 %). LRMS ($M+H^+$) m/z calculated 541.2, found 541.1. ^1H NMR (CD_3OD, 400 MHz) δ 7.88 (s, 1 H), 7.76 (s, 1 H), 7.73-7.69 (m, 2 H), 7.57 (d, 1 H), 7.54-7.51 (m, 1 H), 7.42-7.39 (m, 3 H), 7.23 (dd, 4 H), 6.58 (d, 1 H) , 6.40 (t, 1 H), 6.20 (s, 1 H), 5.18 (s, 2 H), 4.03 (s, 2 H), 3.81 (s, 3 H).

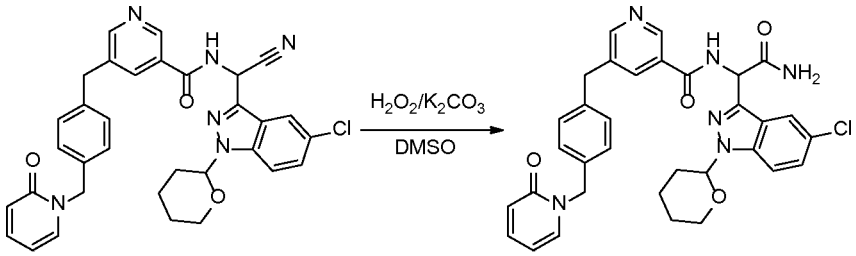
Example 35: Preparation of methyl 2-(5-chloro-1H-indazol-3-yl)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)acetate



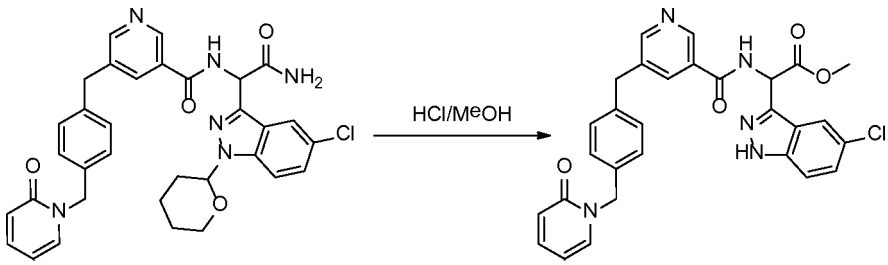
methyl 2-(5-chloro-1H-indazol-3-yl)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)acetate



A mixture of 2-amino-2-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)acetonitrile (290 mg, 1 mmol, 1 eq), 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (320 mg , 1 mmol, 1.0 eq), HATU (500 mg, 1.3 mmol, 1.3 eq), and DIPEA (1 mL) in DMF (5 mL) was stirred at 50 °C overnight. The mixture was mixed with water (20 mL) and filtered. The solid was collected and purified on silica gel column to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)(cyano)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow solid (529 mg, 89%).



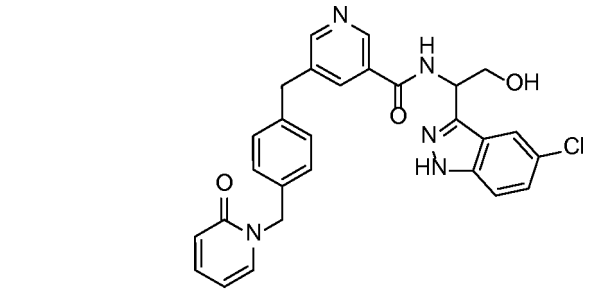
To the solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)(cyano)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (237 mg, 0.4 mmol, 1.0 eq) in DMSO (5 mL) was added K_2CO_3 (28 mg, 0.2 mmol, 0.5 eq) and H_2O_2 (30% aq., 0.5 mL). The mixture was stirred at rt overnight and purified via prep-MPLC to afford N-(2-amino-1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-2-oxoethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (150 mg, 61.4%).



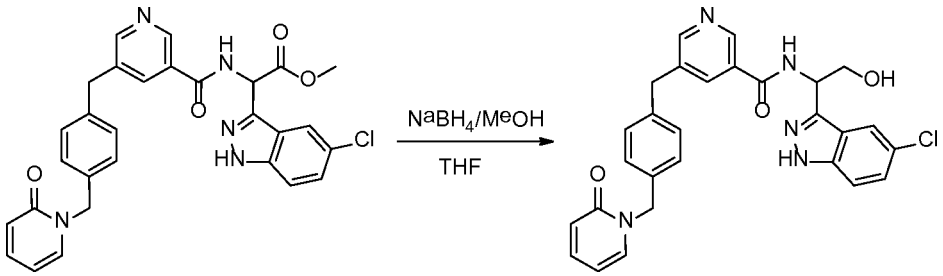
A solution of N-(2-amino-1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-2-oxoethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (110 mg, 0.18 mmol, 1 eq.) in HCl/ MeOH (5 N, 5 mL) was stirred at rt overnight, then concentrated. The residue was purified via prep-MPLC and further purified via prep-TLC (DCM/MeOH = 20/1, v/v) to afford methyl 2-(5-chloro-1H-indazol-3-yl)-2-(5-(4-((2-

oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)acetate as a white solid (60 mg, 61 %). LRMS ($M+H^+$) m/z calculated 542.2, found 542.2. ^{1}H NMR (CD3OD, 300 MHz) δ 8.85 (d, 1 H), 8.57 (d, 1 H), 8.12 (s, 1 H), 7.85 (d, 1 H), 7.68 (dd, 1 H), 7.57-7.50 (m, 2 H), 7.40 (dd, 1 H), 7.25 (dd, 4 H), 6.57 (d, 1 H), 6.38 (t-d, 1 H), 6.20 (s, 1 H), 5.17 (s, 2 H), 4.07 (s, 2 H), 3.80 (s, 3 H).

Example 36: Preparation of N-(1-(5-chloro-1H-indazol-3-yl)-2-hydroxyethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

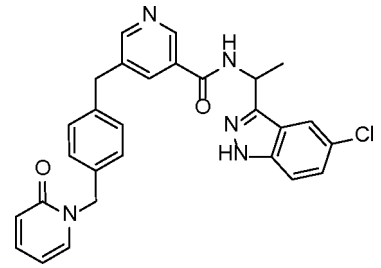


N-(1-(5-chloro-1*H*-indazol-3-yl)-2-hydroxyethyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

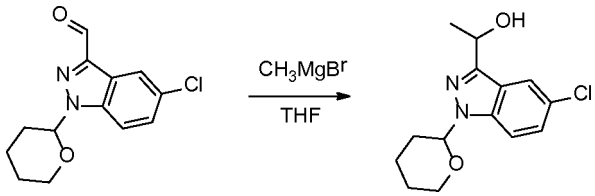


To the solution of methyl 2-(5-chloro-1H-indazol-3-yl)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)acetate (82 mg, 0.15 mmol, 1.0 eq) and $NaBH_4$ (42 mg, 1.1 mmol, 7 eq) in THF (4 mL) was added MeOH (0.3 mL) dropwise at 55 °C. The mixture was stirred at 60 °C for 1 h, cooled to rt and quenched with water (7 drops). Filtered and the filtrate was concentrated. The residue was purified via prep-HPLC to afford N-(1-(5-chloro-1H-indazol-3-yl)-2-hydroxyethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (22 mg, 28.2%). LRMS ($M+H^+$) m/z calculated 514.2, found 514.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.83 (d, 1 H), 8.52 (s, 1 H), 8.22 (s, 1 H), 7.75 (d, 1 H), 7.56 (dd, 1 H), 7.43-7.37 (m, 2 H), 7.23 (dd, 1 H), 7.15 (dd, 4 H), 6.44 (d, 1 H), 6.26 (t, 1 H), 5.60 (t, 1 H), 5.05 (s, 2 H), 4.02 (d, 2 H), 4.01 (s, 2 H).

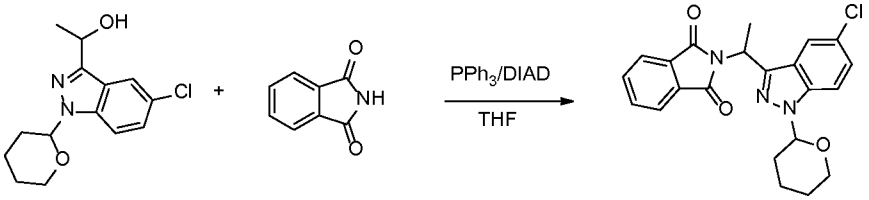
Example 37: Preparation of N-(1-(5-chloro-1H-indazol-3-yl)ethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



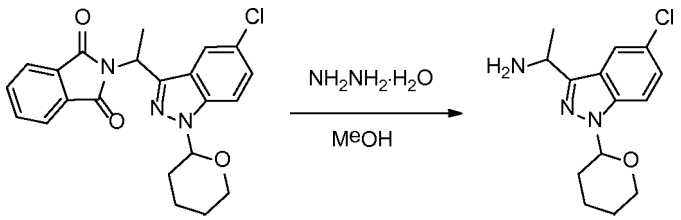
N-(1-(5-chloro-1*H*-indazol-3-yl)ethyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



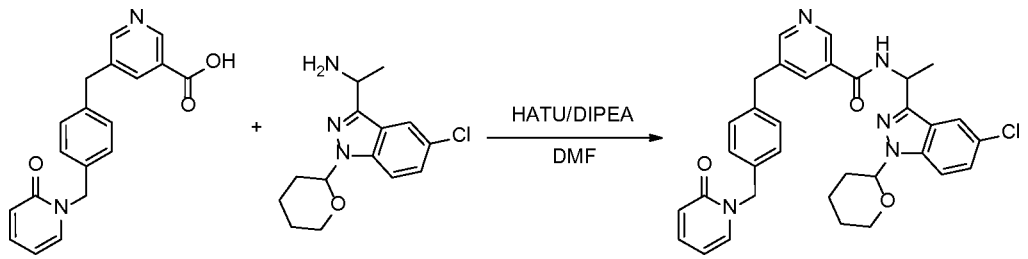
To the solution of 5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-3-carbaldehyde (260 mg, 0.98 mmol, 1.0 eq.) in THF (5 mL) was added a solution of CH_3MgBr in THF (3 mol/L, 0.5 mL, 1.5 eq). The mixture was stirred at rt overnight. The mixture was quenched with water (10 mL) and extracted with EA (20 mL X 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography (PE/EA = 10/1, v/v) to afford 1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethanol as a white solid (270 mg, 97.9%).



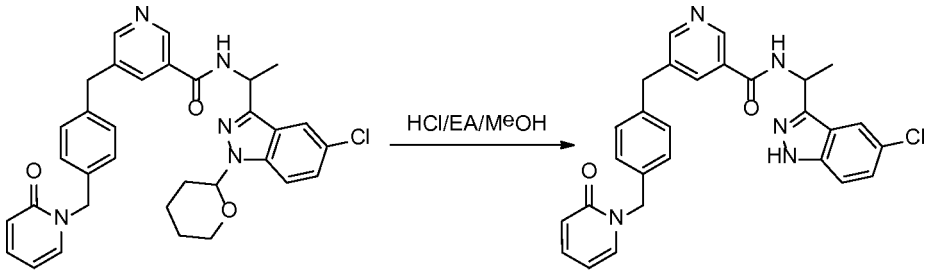
To the solution of 1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethanol (280 mg, 1.0 mmol, 1.0 eq), isoindoline-1,3-dione (156 mg, 1.06 mmol, 1.06 eq), PPh_3 (314 mg, 1.2 mmol, 1.2 eq) in THF (10 mL) was added DIAD (0.3 mL, 1.5 eq) at 0 °C. The mixture was stirred at rt overnight and partitioned between EA (20 mL) and water (10 mL). The aqueous layer was extracted with EA (20 mL X 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via prep-TLC (PE/EA = 7/1, v/v) to afford 2-(1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethyl)isoindoline-1,3-dione as a white solid (150 mg, 36.6%).



To a solution of 2-(1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethyl)isoindoline-1,3-dione (70 mg, 0.18 mmol, 1.0 eq.) in MeOH (4 mL) was added $NH_2NH_2 \cdot H_2O$ (0.10 mL). The mixture was stirred at rt for 3 h. The volatiles were concentrated and to the residue was added DCM (10 mL) and stirred at rt for 1 h, then filtered through Celite. The filtrate was concentrated to afford 1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethanamine as a white solid (54 mg crude, quant).

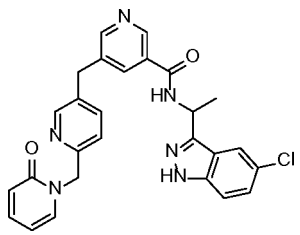


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (58 mg, 0.18 mmol, 1 eq), 1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethanamine (54 mg , 0.18 mmol, 1.0 eq), HATU (69 mg, 0.18 mmol, 1.0 eq), and DIPEA (0.3 mL) in DMF (5 mL) was stirred at rt overnight. The mixture was purified via prep- MPLC to afford N-(1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (58 mg, 61%).

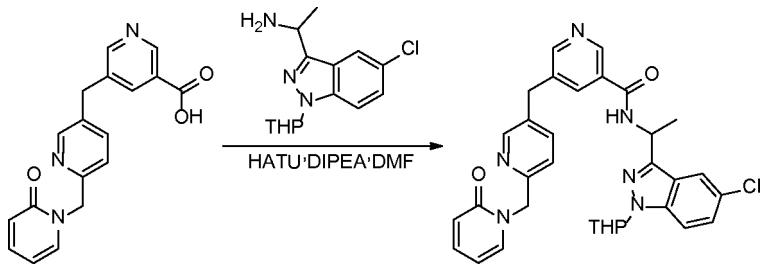


To a solution of N-(1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (58 mg, 0.1 mmol, 1 eq) in MeOH (5 mL) was added HCl/EA (5 N, 3 mL) and the mixture was stirred at rt overnight. The volatiles were concentrated and to the residue was added NH_3/MeOH (3 N, 5 mL) and concentrated again. The rresidue was purified via prep-TLC (MeOH/DCM = 1/15, v/v) to afford N-(1-(5-chloro-1H-indazol-3-yl)ethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow solid (35 mg, 71.4%). LRMS ($M+H^+$) m/z calculated 498.2, found 498.2. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.09 (s, 1 H), 9.14 (d, 1 H), 8.86 (s, 1 H), 8.61 (s, 1 H), 8.05 (s, 1 H), 7.86 (s, 1 H), 7.74 (d, 1 H), 7.53 (d, 1 H), 7.40 (t, 1 H), 7.32 (d, 1 H), 7.25 -7.18 (m, 4 H), 6.38 (d, 1 H), 6.20 (t, 1 H), 5.62 (t, 1 H), 5.03 (s, 2 H), 3.99 (s, 2 H), 1.65 (d, 3 H).

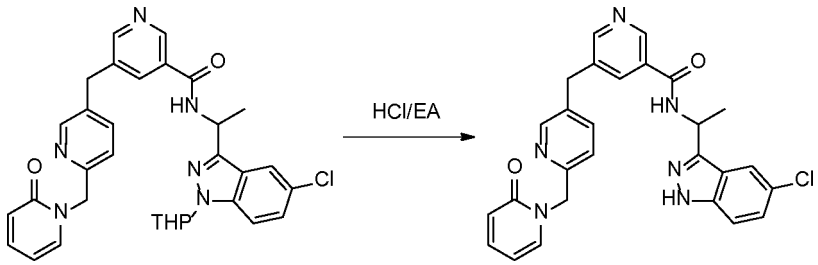
Example 38: Preparation of N-(1-(5-chloro-1H-indazol-3-yl)ethyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide



N-(1-(5-chloro-1*H*-indazol-3-yl)ethyl)-5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamide

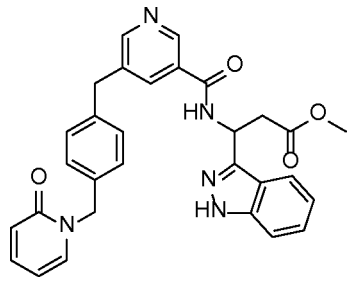


To a solution of 5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinic acid (500 mg crude, 0.5 mmol, 1.0 eq) in DMF (5 mL) were added DIPEA (194 mg, 1.5 mmol, 3.0 eq) and HATU (228 mg, 0.6 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, 1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethanamine (170 mg crude, 0.5 mmol, 1.0 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-(1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide as a yellow solid (130 mg, 45%).

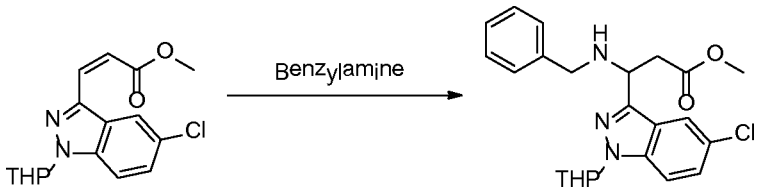


To a solution of N-(1-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)ethyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide (130 mg, 0.22 mmol, 1.0 eq) in MeOH (5 mL) was added HCl/EA (5 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL), neutralized with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-(1-(5-chloro-1H-indazol-3-yl)ethyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide as a white solid (70 mg, 64%). LRMS ($M+H^+$) m/z caculated 499.1, found 499.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.03 (brs, 1 H), 9.12 (d, 1 H), 8.87 (d, 1 H), 8.65 (d, 1 H), 8.47 (d, 1 H), 8.06 (t, 1 H), 7.86 (d, 1 H), 7.75 (dd, 1 H), 7.64 (dd, 1 H), 7.53 (d, 1 H), 7.48-7.40 (m, 1 H), 7.33 (dd, 1 H), 7.13 (d, 1 H), 6.37 (d, 1 H), 6.23 (td, 1 H), 5.63 (t, 1 H), 5.12 (s, 2 H), 4.03 (s, 2 H), 1.66 (d, 3 H).

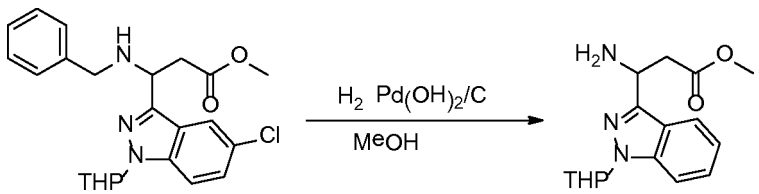
Example 39: Preparation of methyl 3-(1H-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)propanoate



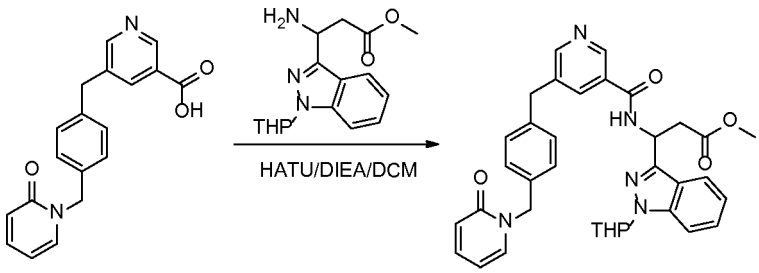
methyl 3-(1*H*-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamido)propanoate



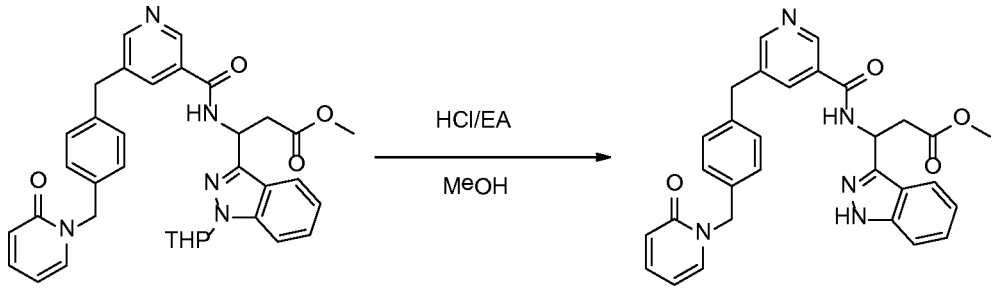
Methyl 3-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)acrylate (200 mg, 0.62 mmol, 1.0 eq) and benzylamine (1 mL) were combined and then heated to 70 °C under N_2 overnight. After cooled to rt, the residue was purified by flash chromatography (MeCN/H_2O = 1/2 to 19/1) to afford methyl 3-(benzylamino)-3-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate as an oil (188 mg, 70%).



A mixture of methyl 3-(benzylamino)-3-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate (140 mg, 0.32 mmol, 1.0 eq), 20% $Pd(OH)_2/C$ (50 mg) in methanol (20 mL) was stirred at rt under a hydrogen atmosphere (1 atm, balloon) for 1.5 h. The reaction mixture was filtered and the filtrate was concentrated to afford methyl 3-amino-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate as a yellow oil (90 mg, 90%).

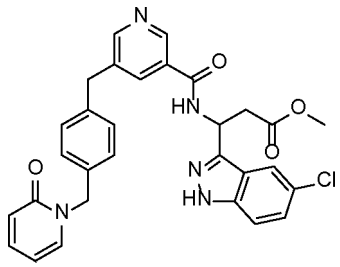


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (95 mg, 0.29 mmol, 1.0 eq), methyl 3-amino-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate (90 mg, 0.29 mmol, 1.0 eq), HATU (113 mg, 0.29 mmol, 1.0 eq) and DIEA (1 mL) in DCM (20 mL) was stirred at rt for 3 h. The mixture was diluted with DCM (50 mL), washed with saturated $NaHCO_3$ (25 mL), and the brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was then further purified by flash chromatography (MeCN/H_2O = 1/4 to 4/1) to afford methyl 3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate as a white solid (129 mg, 72%).

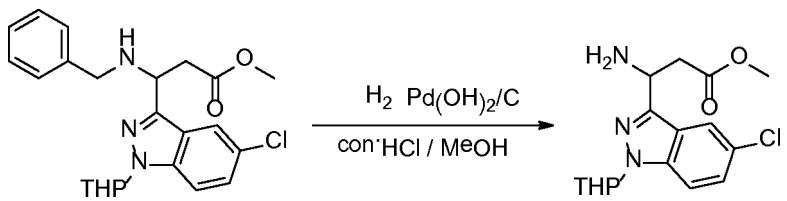


A solution of methyl 3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate (125 mg, 0.20 mmol, 1.0 eq) in MeOH (3 mL) and HCl/EA (3 N, 5 mL) was stirred at 50 °C for 2 h. Then the mixture was concentrated. The residue was purified by flash chromatography (MeCN/H_2O = 1/2 to 19/1) to afford methyl 3-(1H-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)propanoate as a white solid (82 mg, 76%). LRMS ($M+H^+$) m/z calculated 522.2, found 522.2. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.90 (s, 1H), 9.217 (d, 1H), 8.84 (s, 1H), 8.61 (s, 1H), 8.02 (s, 1H), 7.76-7.71 (m, 2H), 7.49 (d, 1H), 7.42-7.29 (m, 2H) , 7.21 (m, 4H), 7.07-7.02 (m, 1H), 6.38 (d, 1H), 6.23-6.18 (m, 1H), 6.02-5.99 (m, 1H), 5.03 (s, 2H), 3.97 (s, 2H), 3.55 (s, 3H), 3.36-3.28 (m, 1H), 3.12-3.04 (m, 1H).

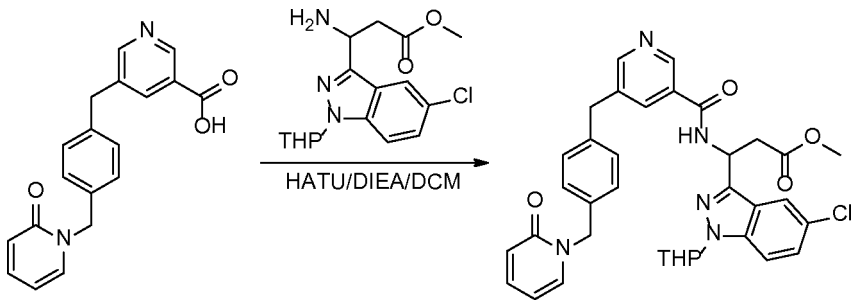
Example 40: Preparation of methyl 3-(5-chloro-1H-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)propanoate



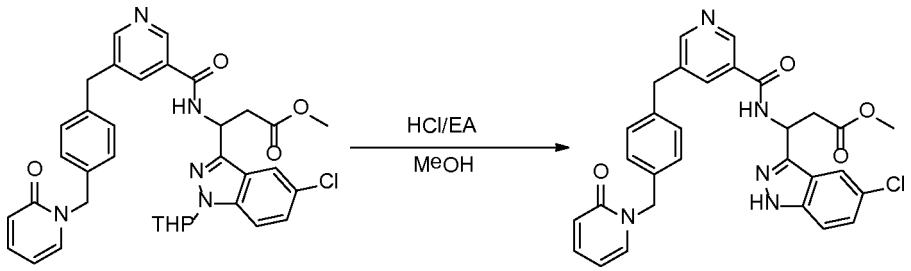
methyl 3-(5-chloro-1*H*-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamido)propanoate



A mixture of methyl 3-(benzylamino)-3-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate (140 mg, 0.32 mmol, 1.0 eq), 20% $Pd(OH)_2$/C (50 mg), conc HCl (0.5 mL) in methanol (25 mL) was stirred at rt under a hydrogen atmosphere (1 atm, balloon) for 1 h. The reaction mixture was filtered and the filtrate was concentrated to afford methyl 3-amino-3-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate as a yellow oil (76 mg, 64%).

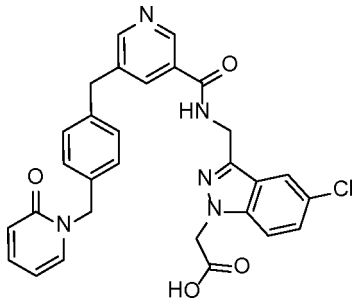


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (70 mg, 0.21 mmol, 1.0 eq), methyl 3-amino-3-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)propanoate (73 mg, 0.21 mmol, 1.0 eq), HATU (83 mg, 0.21 mmol, 1.0 eq) and DIEA (0.5 mL) in DCM (20 mL) was stirred at rt for 2 h.The mixture was diluted with DCM (30 mL), washed with saturated $NaHCO_3$ (20 mL), and the brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was then further purified by flash chromatography ($MeCN/H_2O$ = 1/2 to 19/1) to afford methyl 3-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)propanoate as a white solid (25 mg, 17%).

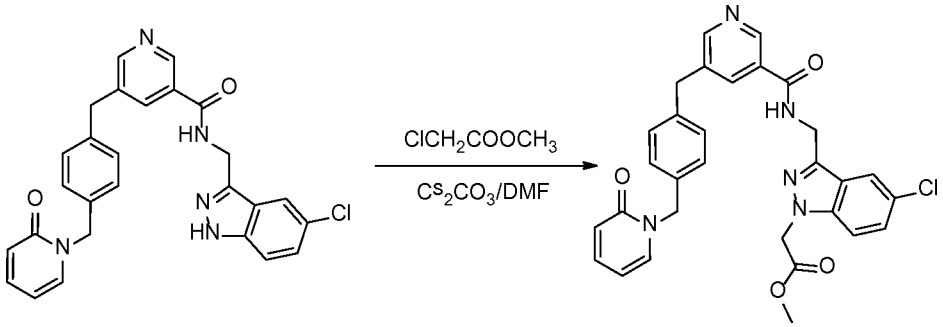


A solution of methyl 3-(5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)propanoate (25 mg, 0.039 mmol, 1.0 eq) in MeOH (2 mL) and HCl/MeOH (2 N, 3 mL) was stirred at rt overnight. Then the mixture was concentrated. The residue was purified by flash chromatography ($MeCN/H_2O$ = 1/19 to 3/2) to afford methyl 3-(5-chloro-1H-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)propanoate as a white solid (16 mg, 73%). LRMS ($M+H^+$) m/z calculated 556.2, found 556.2. ^1H NMR (DMSO-*d6*, 300 MHz) δ 13.11 (s, 1H), 9.18 (d, 1H), 8.81 (d, 1H), 8.62 (d, 1H), 8.02 (s, 1H), 7.82 (s, 1H), 7.73 (dd, 1H), 7.53 (d, 1H), 7.41-7.31 (m, 2H) , 7.23-7.19 (m, 4H), 6.38 (d, 1H), 6.21-6.18 (m, 1H), 5.96-5.91 (m, 1H), 5.03 (s, 2H), 3.97 (s, 2H), 3.55 (s, 3H), 3.31-3.27 (m, 1H), 3.15-3.09 (m, 1H).

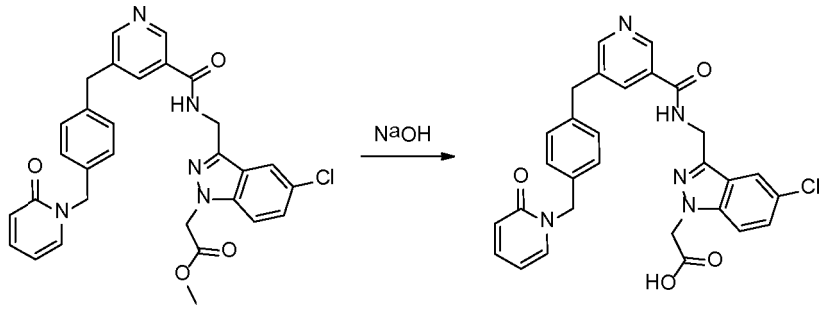
Example 41: Preparation of 2-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid



2-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid

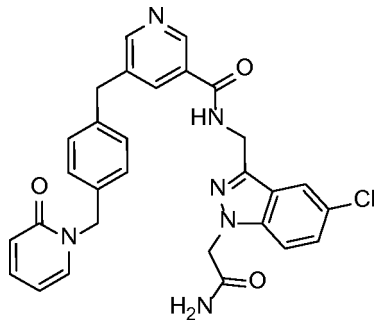


The mixture of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide HCl salt (260 mg, 0.5 mmol, 1.0 eq), methyl 2-chloroacetate (543 mg, 2.5 mmol, 5.0 eq) and Cs_2CO_3 (1.0 g, 3 mmol, 6 eq) in DMF (5 mL) was was stirred at rt overnight. The mixture was poured into water and the precipitate was collected by suction to afford methyl 2-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)acetate as a yellow solid (200 mg, 72.2%).

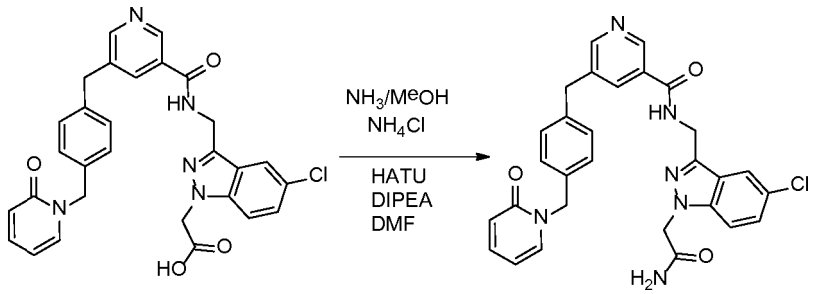


To the solution of methyl 2-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)acetate (200 mg, 0.36 mmol, 1 eq) in THF/MeOH (5 mL/10 mL) was added NaOH aqueous solution (1 N, 5 mL) and the mixture was stirred at rt overnight, then concentrated. The residue was acidified with HCl to pH 3. The mixture was concentrated and the residue was purified via prep-MPLC to afford 2-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid as a yellow solid (140 mg, 74.3 %). LRMS ($M+H^+$) m/z calculated 542.2, found 542.1. ^1H NMR (DMSO-d6, 300 MHz) δ 13.14 (s, 1H), 9.34 (t, 1H), 8.86 (s, 1 H), 8.62 (s, 1 H), 8.05 (s, 1 H), 7.93 (s, 1 H), 7.75 (d, 1 H), 7.67 (d, 1 H), 7.42-7.37 (m, 2 H), 7.25-7.19 (m, 4 H), 6.38 (d, 1 H), 6.21 (t, 1 H), 5.24 (s, 2 H), 5.03 (s, 2 H), 4.76 (d, 2 H), 3.99 (s, 2 H).

Example 42: Preparation of N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

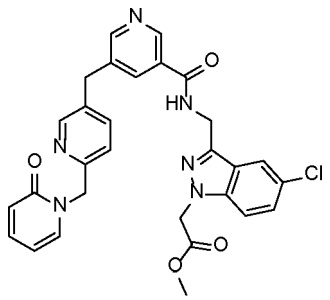


N-((1-(2-amino-2-oxoethyl)-5-chloro-1*H*-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

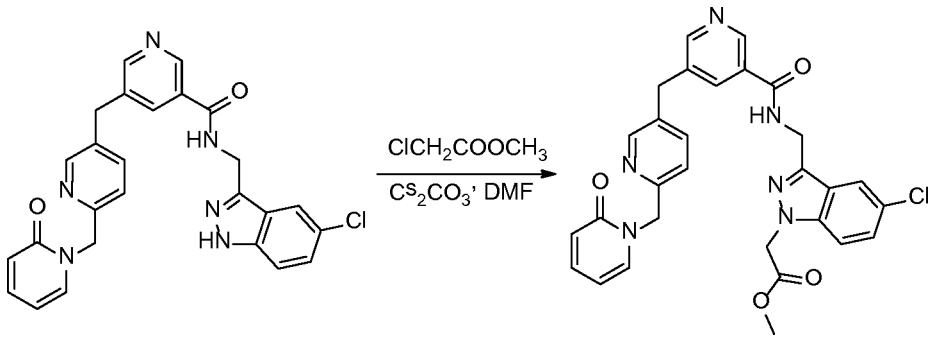


A mixture of 2-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid (110 mg, 0.20 mmol, 1 eq), NH_3/MeOH (3 mol/L, 0.5 mL), NH_4Cl (20 mg, 0.37 mmol, 1.9 eq), HATU (80 mg, 0.21 mmol, 1.05 eq), DIPEA (0.3 mL) in DMF (3 mL) was stirred at rt overnight. The mixture was purified via flash chromatography to afford N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (41 mg, 37.3%).. LRMS ($M+H^+$) m/z calculated 542.0, found 542.1. ^{1}H NMR (DMSO-d6, 300 MHz) δ 9.33 (t, 1H), 8.86 (s, 1 H), 8.61 (s, 1 H), 8.06 (s, 1 H), 7.86 (s, 1 H), 7.74 (d, 1 H), 7.45-7.37 (m, 3 H), 7.31-7.19 (m, 6 H), 6.39 (d, 1 H), 6.21 (t, 1 H), 5.04 (s, 2 H), 4.74 (s, 4 H), 3.98 (s, 2 H).

Example 43: Preparation of methyl 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetate

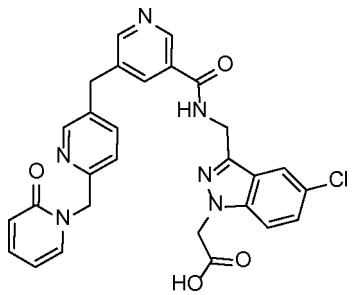


methyl 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1*H*-indazol-1-yl)acetate

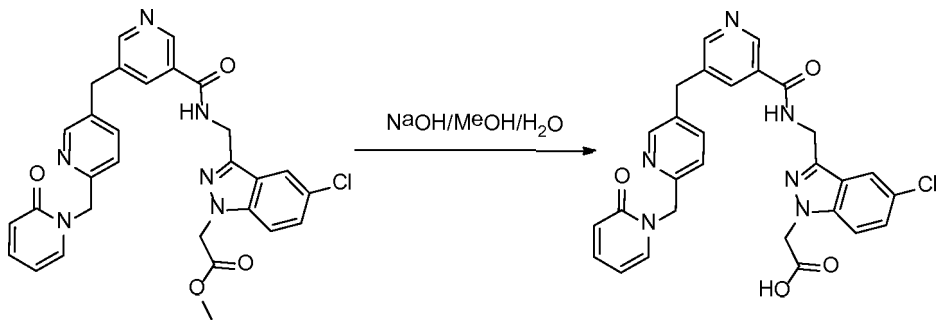


To a solution of N-((5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide (200 mg crude, 0.41 mmol, 1.0 eq) in DMF (4 mL) were added methyl 2-chloroacetate (445 g, 4.1 mmol, 10.0 eq) and Cs_2CO_3 (668 mg, 2.05 mmol, 5.0 eq). The mixture was stirred at rt overnight. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford methyl 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetate as a yellow solid (80 mg, 35%). LRMS ($M+H^+$) m/z caculated 557.1, found 557.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.34 (t, 1 H), 8.88 (d, 1 H), 8.66 (d, 1 H), 8.47 (d, 1 H), 8.08 (d, 1 H), 7.94 (d, 1 H), 7.74 (dd, 1 H), 7.67 (d, 1 H), 7.64 (dd, 1 H), 7.48-7.40 (m, 2 H), 7.13 (d, 1 H), 6.37 (d, 1 H), 6.23 (td, 1 H), 5.38 (s, 2 H), 5.12 (s, 2 H), 4.76 (d, 2 H), 4.03 (s, 2 H), 3.76 (s, 3 H).

Example 44: Preparation of 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid



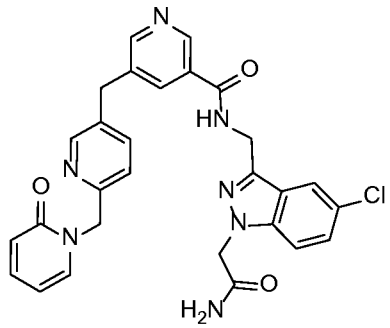
2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid



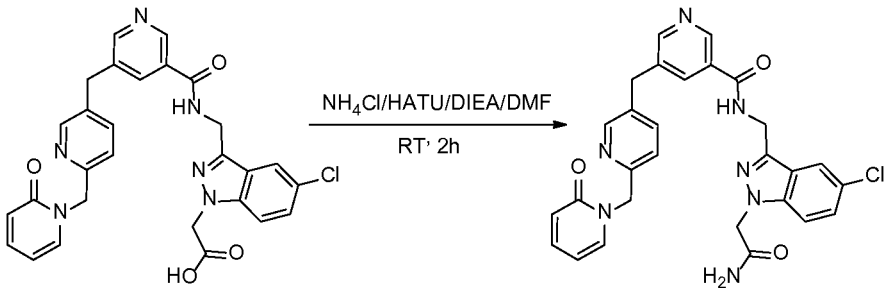
The solution of methyl 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetate (80 mg, 0.14 mmol, 1.0 eq) in MeOH (2 mL) and THF (2 mL) was treated with an aqueous solution of NaOH (56 mg, 1.4 mmol, 10 eq) in 2 mL of water. The

mixture was stirred at rt overnight. Then the mixture was concentrated and the residue was acidified with 1 N HCl till pH was 3. The mixture was purified by flash chromatography to give 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid as a yellow solid (29 mg, 38%). LRMS ($M+H^+$) m/z calculated 543.15, found 543.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.34 (t, 1H), 8.88 (s, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 7.92 (s, 1H), 7.74 (d, 1H), 7.64 (d, 2H), 7.45-7.39 (m, 2H), 7.13 (d, 1H), 6.37 (d, 1H), 6.23 (t, 1H), 5.18 (s, 2H), 5.12 (s, 2H), 4.76 (d, 2H), 4.03 (s, 2H).

Example 45: Preparation of N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide

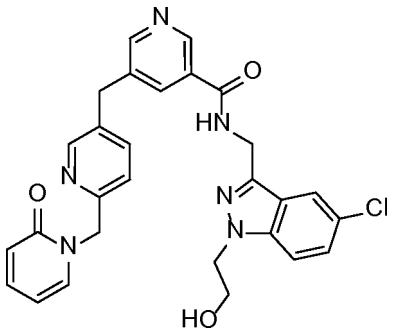


N-((1-(2-amino-2-oxoethyl)-5-chloro-1*H*-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamide

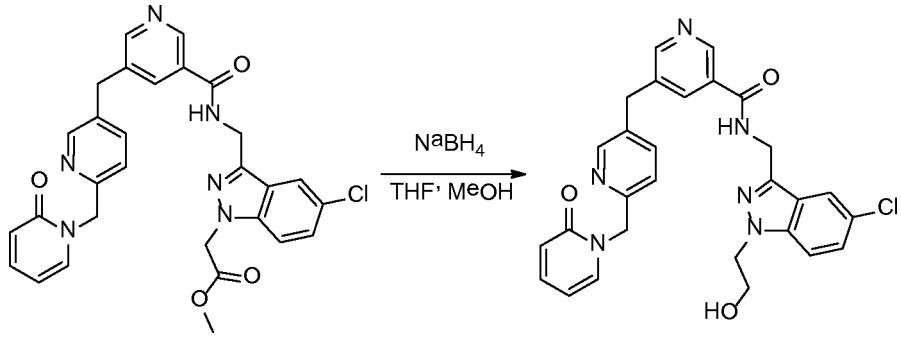


A mixture of 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid (22 mg, 0.04 mmol, 1.0 eq), NH_4Cl (3.3 mg, 0.06 mmol, 1.5 eq), HATU (30.4 mg, 0.08 mmol, 2.0 eq) and DIEA (15 mg, 0.12 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt for 2 h. The mixture was poured into water (20 mL) and extracted with EtOAc (20 mL x2). The combined organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated. The obtained residue was purified by flash columm to afford N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide as a yellow solid (7 mg, 32%). LRMS ($M+H^+$) m/z calculated 542.17, found 542.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.32 (t, 1H), 8.76 (s, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.74 (d, 1H), 7.65-7.60 (m, 3H), 7.43-7.38 (m, 2H), 7.30 (s, 1H), 7.13 (d, 1H), 6.37 (d, 1H), 6.23 (t, 1H), 5.12 (s, 2H), 5.03 (s, 2H), 4.76 (d, 2H), 4.03 (s, 2H).

Example 46: Preparation of N-((5-chloro-1-(2-hydroxyethyl)-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide

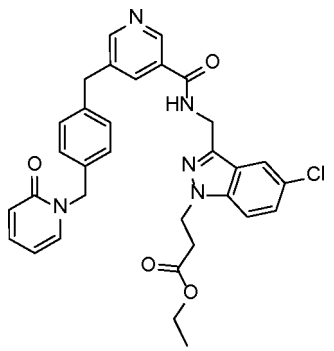


N-((5-chloro-1-(2-hydroxyethyl)-1*H*-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamide

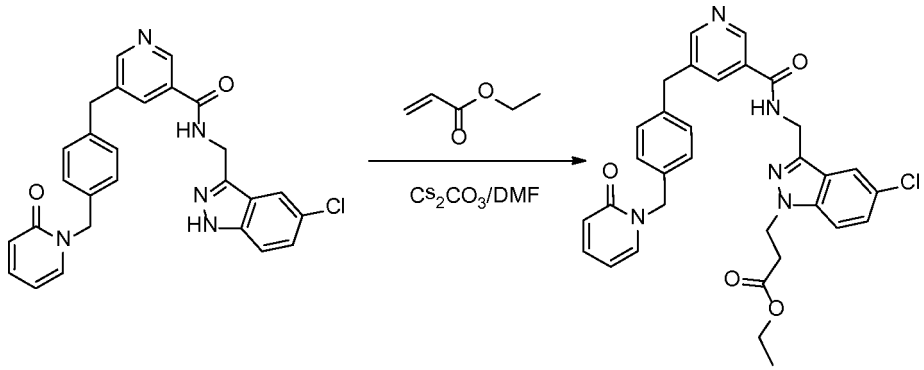


To a solution of methyl 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetate (80 mg, 0.14 mmol, 1.0 eq) in THF (10 mL) was added $NaBH_4$ (33 mg, 0.86 mmol, 6.0 eq). The mixture was heated at 60 °C. The mixture was added dropwise MeOH (2 mL) over 1 h and then heated at 60 °C for 1 h. The mixture was added water (5 mL). The mixture was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford 20 mg product, which was further purified via prep-HPLC to afford N-((5-chloro-1-(2-hydroxyethyl)-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide as a yellow solid (7 mg, 9%). LRMS ($M+H^+$) m/z caculated 529.1, found 529.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.75 (d, 1 H), 8.50 (s, 1 H), 8.33 (s, 1 H), 7.98 (s, 1 H), 7.74 (d, 1 H), 7.64 (dd, 1 H), 7.55 (dd, 1 H), 7.50-7.40 (m, 2 H), 7.25 (dd, 1 H), 7.14 (d, 1 H), 6.44 (d, 1 H), 6.31 (t, 1 H), 5.13 (s, 2 H), 4.77 (s, 2 H), 4.34 (t, 2 H), 4.00 (s, 2 H), 3.84 (t, 2 H).

Example 47: Preparation of ethyl 3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoate

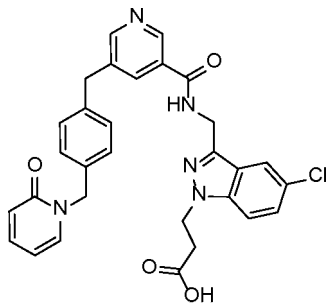


ethyl 3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamido)methyl)-1*H*-indazol-1-yl)propanoate

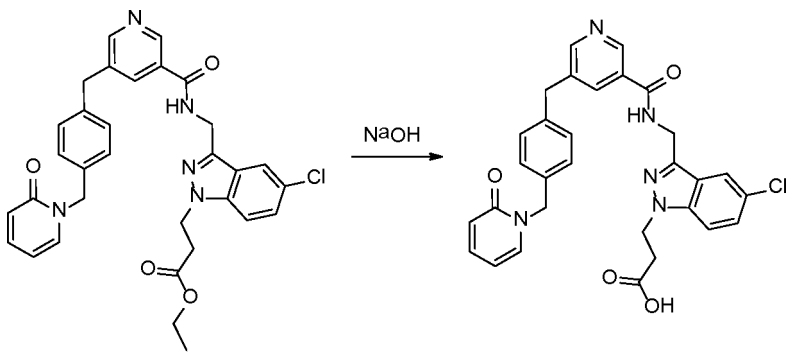


The mixture of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide HCl salt (260 mg, 0.5 mmol, 1.0 eq), ethyl acrylate (250 mg, 2.5 mmol, 5 eq) and Cs_2CO_3 (815 mg, 2.5 mmol, 5.0 eq) in DMF (3 mL) was was stirred at 80 °C overnight. The mixture was cooled to rt and poured into water (10 mL). The aqueous layer was extracted with DCM (10 mL X3).The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated and the residue was purified via prep-HPLC to afford ethyl 3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoate as a white solid (47 mg, 16.1%). LRMS ($M+H^+$) m/z calculated 584.2, found 584.1. ^1H NMR (CD3OD, 400 MHz) δ 8.83 (d, 1 H), 8.57 (d, 1 H), 8.09 (t, 1 H), 7.85 (d, 1 H), 7.69 (dd, 1 H), 7.62 (s, 1 H), 7.60 (s, 1 H), 7.56-7.51 (m, 1 H), 7.39 (dd, 1 H), 7.26 (dd, 4 H), 6.58 (d, 1 H), 6.40 (t-d, 1 H), 5.18 (s, 2 H), 4.89 (s, 2 H), 4.65 (t, 2 H), 4.08 (s, 2 H), 4.03 (q, 2 H), 2.96 (t, 2 H), 1.11 (t, 3 H).

Example 48: Preparation of 3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoic acid



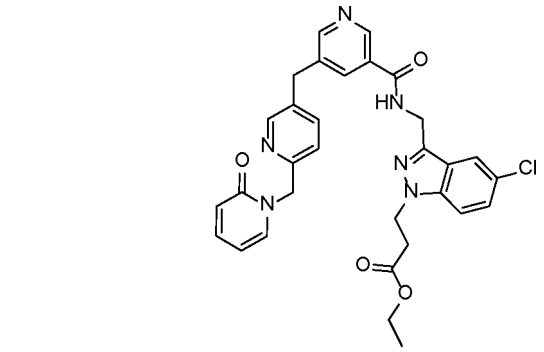
3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamido)methyl)-1*H*-indazol-1-yl)propanoic acid



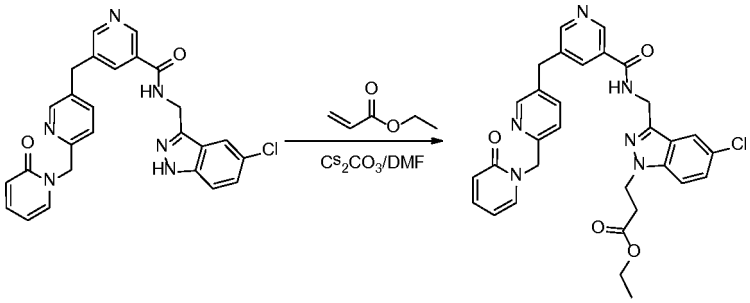
To the solution of ethyl 3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoate (30 mg, 0.05 mmol, 1 eq) in THF/MeOH (1 mL/1 mL) was added NaOH aqueous

solution (1 N, 1 mL) and the mixture was stirred at rt overnight, then concentrated. The residue was acidified with HCl to pH 5. Filtered and the solid was collected to afford 3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoic acid as a white solid (27 mg, 93.1 %). LRMS ($M+H^+$) m/z calculated 556.2, found 556.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.39 (t, 1 H), 8.92 (d, 1 H), 8.69 (d, 1 H), 8.20 (s, 1 H), 7.89 (d, 1 H), 7.75 (dd, 1 H), 7.71 (d, 1 H), 7.42-7.38 (m, 2 H), 7.23 (dd, 4 H), 6.58 (d, 1 H), 6.38 (d, 1 H), 6.21 (t, 1 H), 5.04 (s, 2 H), 4.76 (d, 2 H), 4.55 (t, 2 H), 4.03 (s, 2 H), 2.85 (t, 2 H).

Example 49: Preparation of ethyl 3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoate

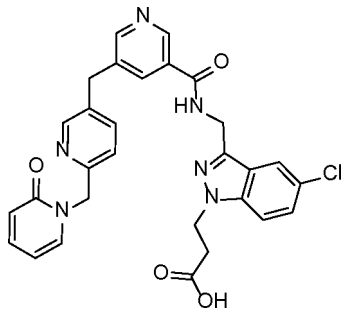


ethyl 3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1*H*-indazol-1-yl)propanoate

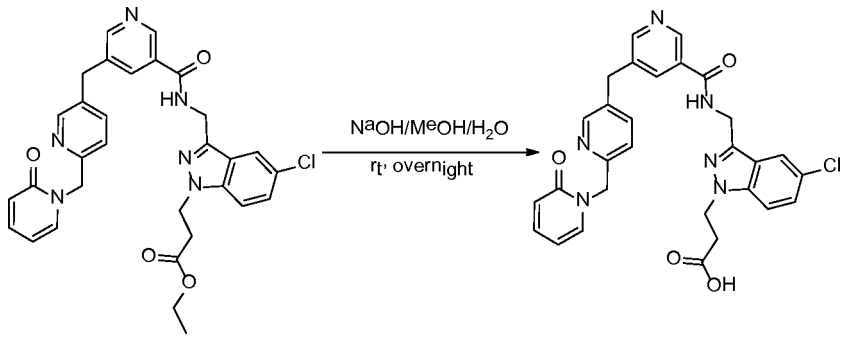


The mixture of N-((5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide (68 mg, 0.14 mmol, 1.0 eq), ethyl acrylate (17 mg, 0.17 mmol, 1.2 eq) and Cs_2CO_3 (55 mg, 0.17 mmol, 1.2 eq) in DMF (5 mL) was stirred at 80 °C for 1 h. The mixture was cooled to rt and purified directly by flash chromatography to afford ethyl 3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoate as a yellow solid (65 mg, 79%). LRMS ($M+H^+$) m/z calculated 585.2, found 585.2. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.86 (s, 1H), 8.60 (s, 1H), 8.44 (s, 1H), 8.09 (s, 1H), 7.84 (s, 1H), 7.75 (d, 1H), 7.64 (d, 1H), 7.59-7.53 (m, 2H), 7.36 (d, 1H), 7.24 (d, 1H), 6.55 (d, 1H), 6.42 (t, 1H), 5.23 (s, 2H), 4.87 (s, 2H), 4.63 (t, 2H), 4.09 (s, 2H), 4.02 (q, 2H), 2.94 (t, 2H), 1.11 (t, 3H).

Example 50: Preparation of 3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoic acid

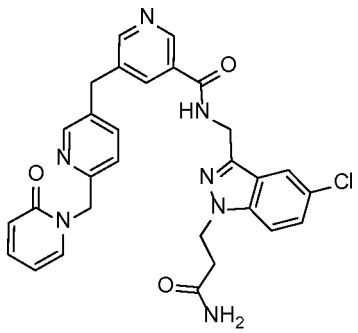


3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1*H*-indazol-1-yl)propanoic acid

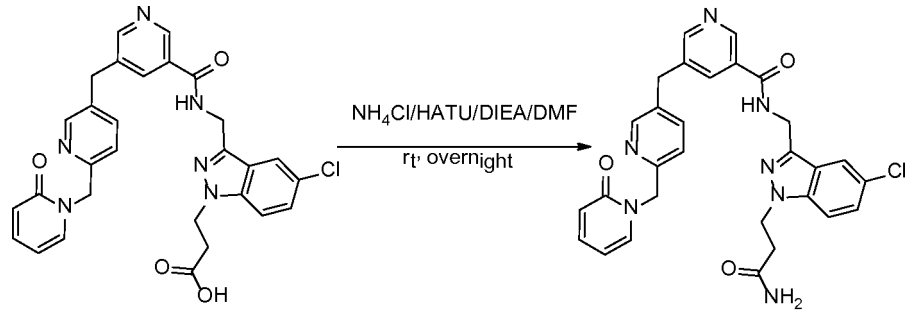


The solution of ethyl 3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoate (76 mg, 0.14 mmol, 1.0 eq) in MeOH (2 mL) was treated with an aqueous solution of NaOH (22 mg, 0.56 mmol, 4.0 eq) in 2 mL of water. The mixture was stirred at rt overnight. Then the mixture was concentrated and the residue was acidified with 1 N HCl till pH was 3. The mixture was purified by flash chromatography to give 3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoic acid as a white solid (58 mg, 74%). LRMS ($M+H^+$) m/z calculated 557.17, found 557.2. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.85 (s, 1H), 8.60 (s, 1H), 8.44 (s, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 7.75 (dd, 1H), 7.65 (dd, 1H), 7.58 (d, 1H), 7.54 (td, 1H), 7.35 (dd, 1H), 7.24 (d, 1H), 6.55 (d, 1H), 6.41 (td, 1H), 5.24 (s, 2H), 4.87 (t, 2H), 4.61 (t, 2H), 4.11 (s, 2H), 2.87 (t, 2H).

Example 51: Preparation of N-((1-(3-amino-3-oxopropyl)-5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide

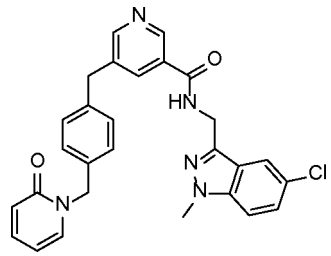


N-((1-(3-amino-3-oxopropyl)-5-chloro-1*H*-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamide

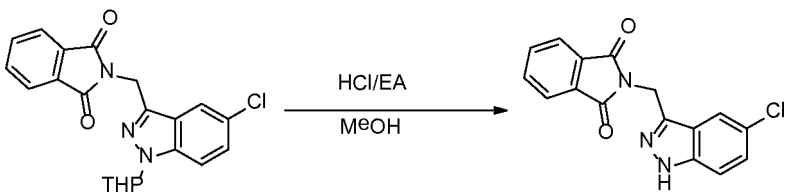


A mixture of 3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoic acid (140 mg, 0.25 mmol, 1.0 eq), NH_4Cl (20 mg, 0.38 mmol, 1.5 eq), HATU (190 mg, 0.5 mmol, 2.0 eq) and DIEA (96 mg, 0.75 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt overnight. The mixture was poured into water (20 mL) and extracted with EtOAc (30 mL x2). The combined organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated. The obtained residue was purified by flash columm to afford N-((1-(3-amino-3-oxopropyl)-5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide as a white solid (91.9 mg, 66%).LRMS ($M+H^+$) m/z calculated 556.19, found 556.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.30 (t, 1H), 8.87 (s, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 8.07 (s, 1H), 7.88 (s, 1H), 7.75-7.63 (m, 3H), 7.46-7.37 (m, 3H), 7.13 (d, 1H), 6.87 (s, 1H), 6.36 (d, 1H), 6.23 (t, 1H), 5.12 (s, 2H), 4.75 (d, 2H), 4.54 (t, 2H), 4.03 (s, 2H), 2.66 (t, 2H).

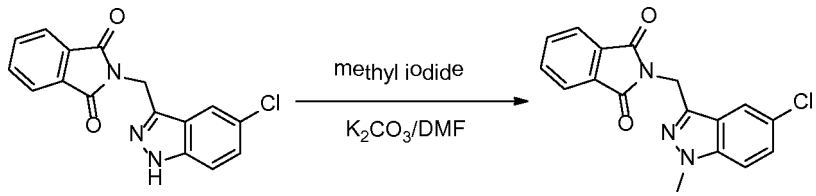
Example 52: Preparation of N-((5-chloro-1-methyl-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



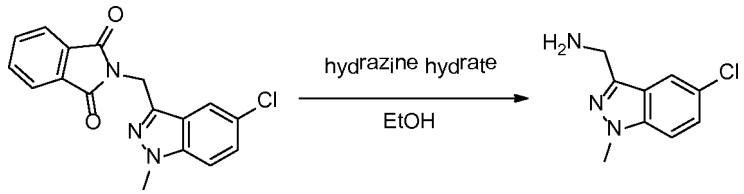
N-((5-chloro-1-methyl-1*H*-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



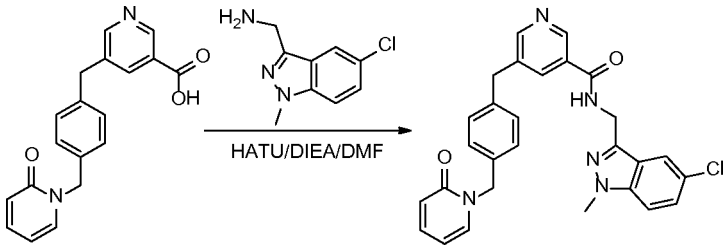
A solution of 2-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)isoindoline-1,3-dione (650 mg, 1.6 mmol, 1.0 eq) in MeOH (10 mL) and HCl/EA (3 N, 20 mL) was stirred at rt for 5 h. Then the mixture was concentrated in vacuo to afford 2-((5-chloro-1H-indazol-3-yl)methyl)isoindoline-1,3-dione as a white solid (500 mg, 87%).



To a cold suspension of 2-((5-chloro-1H-indazol-3-yl)methyl)isoindoline-1,3-dione (500 mg, 1.4 mmol, 1.0 eq) and K_2CO_3 (396 mg, 2.8 mmol, 2.0 eq) in DMF (5 mL) was added methyl iodide (408 mg, 2.8 mmol, 2.0 eq). The suspension was stirred at rt overnight and then quenched with EA/H_2O (20 mL/20 mL). The precipitate was filtered and dried to afford 2-((5-chloro-1-methyl-1H-indazol-3-yl)methyl)isoindoline-1,3-dione as a white solid (295 mg, 63%).

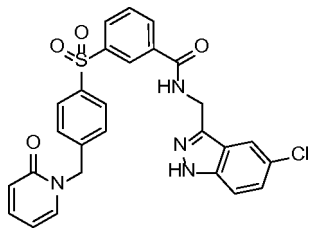


2-((5-Chloro-1-methyl-1H-indazol-3-yl)methyl)isoindoline-1,3-dione (290 mg, 0.89 mmol, 1.0 eq) in ethanol (20 mL) was treated with hydrazine hydrate (1 mL, 31.5 mmol), the mixture was stirred at rt for 20 h. The solid precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (MeCN/H_2O = 1/2 to 9/1) to give (5-chloro-1-methyl-1H-indazol-3-yl)methanamine (162 mg, 93%).

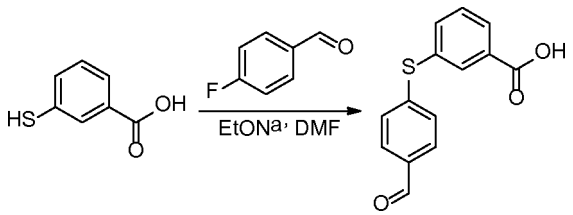


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (150 mg, 0.46 mmol, 1.0 eq), (5-chloro-1-methyl-1H-indazol-3-yl)methanamine (160 mg, 0.81 mmol, 1.7 eq), HATU (213 mg, 0.56 mmol, 1.2 eq) and DIEA (1 mL) in DMF (3 mL) was stirred at rt for 2 h. The mixture was purified by flash chromatography (MeCN/ H_2O = 1/2 to 9/1) to afford N-((5-chloro-1-methyl-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (112 mg, 48%). LRMS ($M+H^+$) m/z calculated 498.2, found 498.2. ^{1}H NMR (DMSO-d6, 300 MHz) δ 9.28 (t, 1H), 8.85 (d, 1H), 8.61 (d, 1H), 8.03 (t, 1H), 7.90 (d, 1H), 7.74 (dd, 1H), 7.65 (d, 1H) , 7.42-7.36 (m, 2H), 7.24-7.18 (m, 4H), 6.38 (d, 1H), 6.22-6.17 (m, 1H), 5.02 (s, 2H), 4.74 (d, 2H), 4.00 (s, 3H), 3.98 (s, 2H).

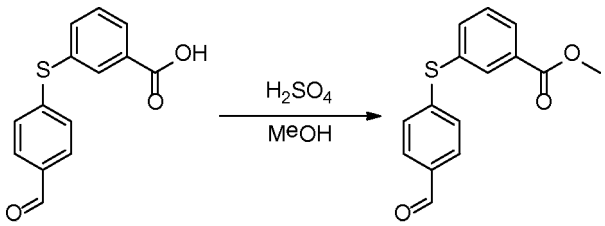
Example 53: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzamide



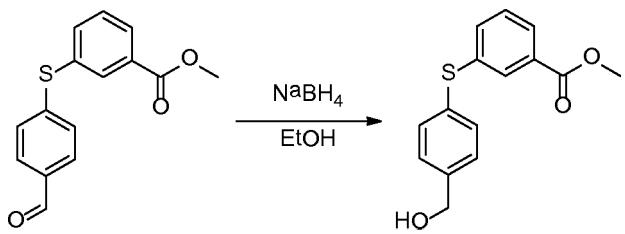
N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzamide



To a solution of 3-mercaptobenzoic acid (0.5 g, 3.3 mmol, 1.0 eq) in DMF (5 mL) was added EtONa (2.1 g, 21% in EtONa, 6.5 mmol, 2.0 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, then 4-fluorobenzaldehyde (0.4 g, 3.3 mmol, 1.0 eq) was added into the mixture. The reaction mixture was stirred at rt overnight. The reaction mixture was poured into ice-water (10 mL), acidified with 1 N HCl to pH 3-4. The mixture was concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (20 mL) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography to afford 3-((4-formylphenyl)thio)benzoic acid as a yellow solid (1.1 g, about 50% purity, 64%).

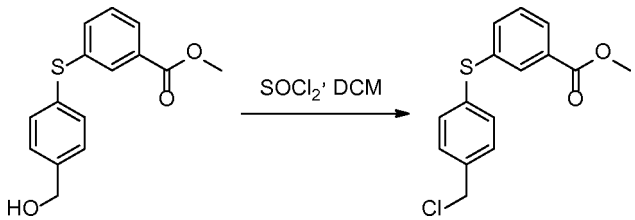


To a solution of 3-((4-formylphenyl)thio)benzoic acid (1.1 g, about 50% purity, 2.2 mmol, 1.0 eq) in MeOH (10 mL) was added H_2SO_4 (0.84 g, 8.6 mmol, 4.0 eq) at rt. The mixture was heated at 80 °C overnight. The mixture was concentrated to remove MeOH, then diluted with ice-water (10 mL) and neutralized with saturated $NaHCO_3$ to pH 7-8. The mixture was concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (20 mL) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography to afford methyl 3-((4-formylphenyl)thio)benzoate as a yellow solid (400 mg, 68%).

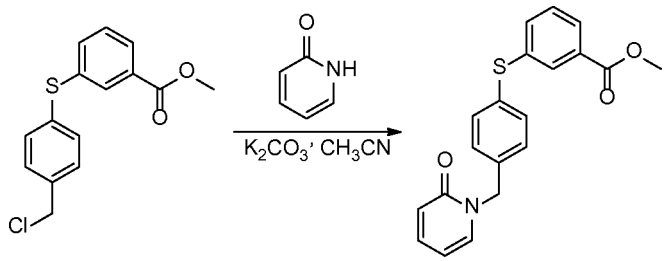


To a solution of methyl 3-((4-formylphenyl)thio)benzoate (400 mg, 1.47 mmol, 1.0 eq) in EtOH (10 mL) was added $NaBH_4$ (67 mg, 1.76 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at rt overnight. The mixture was mixed with water (5 mL). The mixture was concentrated to dryness under reduced pressure. The

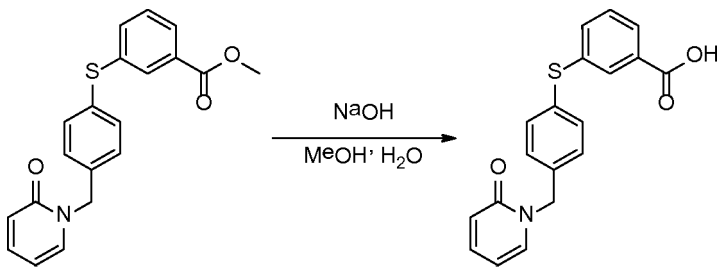
residue was re-dissolved in MeOH (20 mL) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography to afford methyl 3-((4-(hydroxymethyl)phenyl)thio)benzoate as a yellow solid (200 mg, 49%).



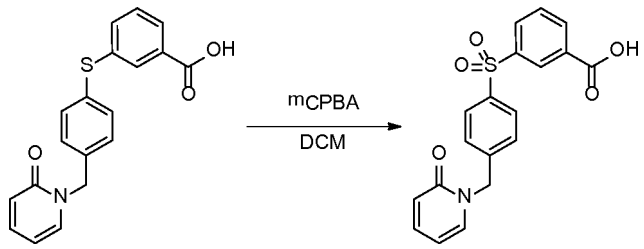
To a solution of methyl 3-((4-(hydroxymethyl)phenyl)thio)benzoate (200 mg, 0.73 mmol, 1.0 eq) in DCM (2 mL) were added $SOCl_2$ (434 mg, 3.65 mmol, 5.0 eq) at 0 °C under N_2. The mixture was stirred at rt for 30 min. The mixture was concentrated to dryness under reduced pressure to afford methyl 3-((4-(chloromethyl)phenyl)thio)benzoate as a yellow oil (200 mg crude, 94%).



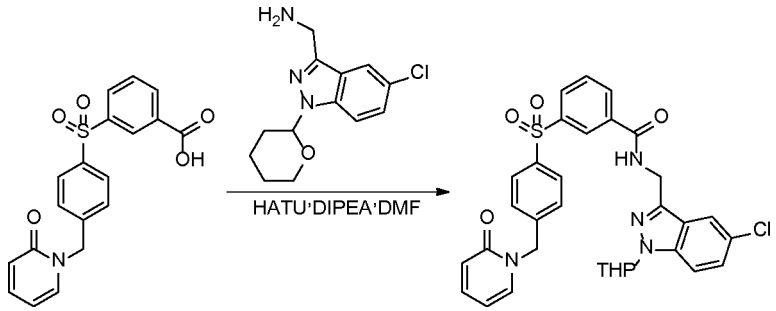
A mixture of methyl 3-((4-(chloromethyl)phenyl)thio)benzoate (200 mg crude, 0.73 mmol, 1.0 eq), pyridin-2(1H)-one (104 mg, 1.1 mmol, 1.5 eq) and K_2CO_3 (302 mg, 2.19 mmol, 3.0 eq) in MeCN (10 mL) was stirred at 80 °C overnight. The mixture was filtered and the filtrate was concentrated to afford methyl 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)thio)benzoate as a yellow solid (300 mg crude, quant).



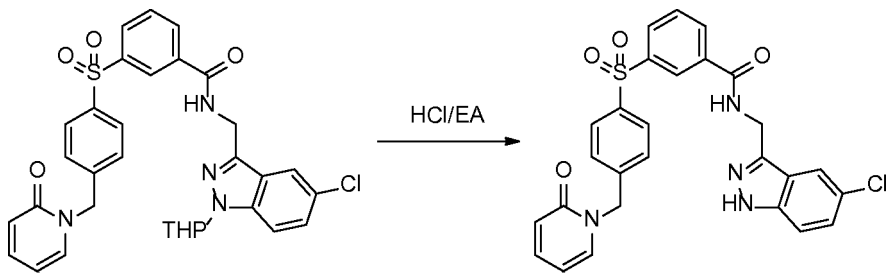
To a solution of methyl 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)thio)benzoate (300 mg crude, 0.73 mmol, 1.0 eq) in MeOH (5 mL) and H_2O (5 mL) was added NaOH (88 mg, 2.19 mmol, 3.0 eq). The mixture was heated at 60 °C for 30 min. The mixture was concentrated to remove MeOH, then diluted with ice-water (10 mL) and acidified with 1 N HCl to pH 3-4. The mixture was concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (10 mL) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography to afford 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)thio)benzoic acid as a white solid (120 mg, 49%).



To a solution of 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)thio)benzoic acid (110 mg, 0.33 mmol, 1.0 eq) in DCM (10 mL) were added m-CPBA (662 mg, 3.3 mmol, 10.0 eq) at rt. The mixture was stirred at rt for 2 h. The mixture was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzoic acid as a white solid (70 mg, 57%).



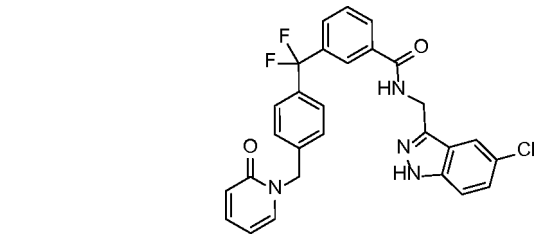
To a solution of 3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzoic acid (70 mg, 0.19 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (81 mg, 0.63 mmol, 3.0 eq) and HATU (96 mg, 0.25 mmol, 1.3 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (61 mg, 0.23 mmol, 1.2 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzamide as a yellow solid (100 mg, 85%).



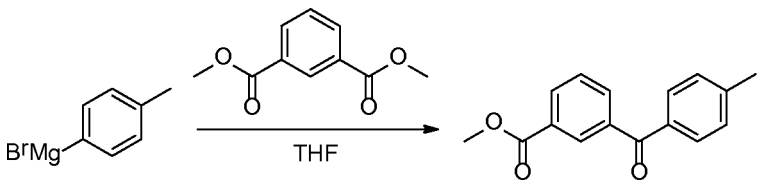
To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzamide (100 mg, 0.16 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/MeOH (2 mL) at 0 °C. The mixture was stirred at rt for 2 h. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL), neutralized with saturated $NaHCO_3$ (10 mL). The aqueous layer was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzamide as a yellow solid (70 mg, 82%). LRMS (M-H) m/z caculated 531.1,

found 531.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.12 (brs, 1 H), 9.44 (t, 1 H), 8.43 (s, 1 H), 8.16 (d, 1 H), 8.08 (d, 1 H), 7.98-7.94 (m, 2 H), 7.90 (s, 1 H), 7.78 (d, 1 H), 7.71 (t, 1 H), 7.55 (d, 1 H), 7.48-7.40 (m, 3 H), 7.33 (dd, 1 H), 6.40 (d, 1 H), 6.25 (t, 1 H), 5.15 (s, 2 H), 4.80 (d, 2 H).

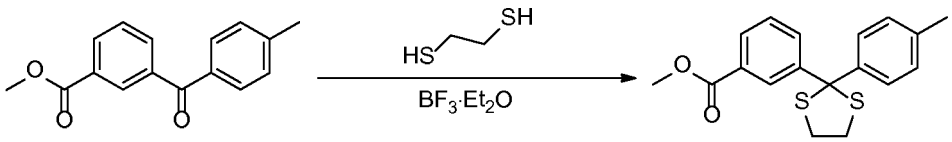
Example 54: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide



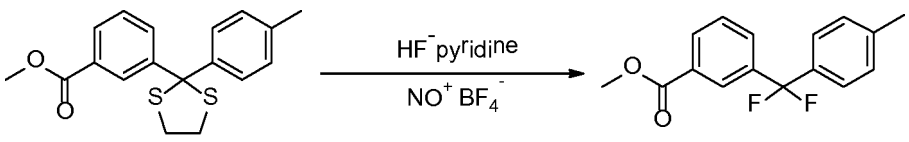
N-((5-chloro-1*H*-indazol-3-yl)methyl)-3-(difluoro(4-((2-oxopyridin-1(2*H*)-yl)methyl)phenyl)methyl)benzamide



To a solution of dimethyl isophthalate (25 g, 129 mmol, 4.3 eq) in dry THF (500 mL) was added p-tolylmagnesium bromide (30 mmol, 1 eq) dropwise under nitrogen in an ice-water bath and the mixture was stirred at this temperature for 4 h. The reaction mixture was poured into aqueous NH_4Cl solution and extracted with EA. The organic layers were concentrated and the residue was purified by flash chromatography to give methyl 3-(4-methylbenzoyl)benzoate as a white solid (1.6 g, 21%).

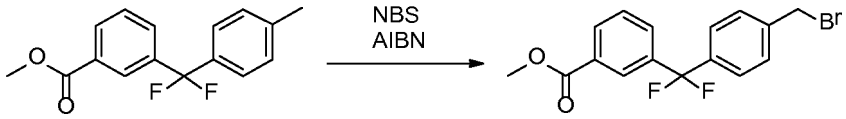


To a solution of methyl 3-(4-methylbenzoyl)benzoate (508 mg, 2 mmol, 1 eq) and $BF_3.Et_2O$ (1.42 g, 10 mmol, 5 eq) in dry DCM (5 mL) was added ethane-1,2-dithiol (954 mg, 8 mmol, 4 eq). The mixture was stirred overnight and then partitioned between DCM and water. The organic layer was concentrated and purified by Prep-TLC (PE/EA = 5/1) to afford methyl 3-(2-(p-tolyl)-1,3-dithiolan-2-yl)benzoate as a white solid (400 mg, 61%).

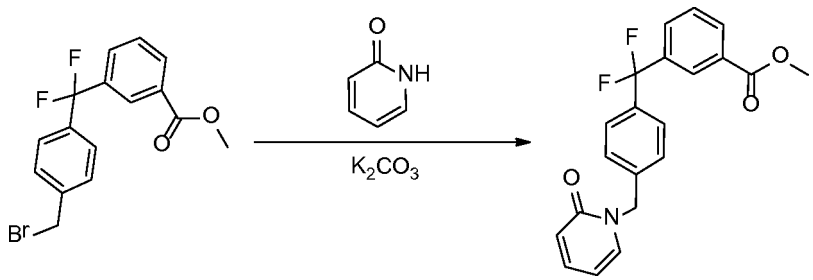


To a solution of $NO^+BF_4^-$ (1 g, 8.5 mmol, 5.7 eq) and 70% HF-pyridine (4.4 g, 31 mmol, 20 eq) in dry DCM (20 mL) at 0 °C was added a solution of methyl 3-(2-(p-tolyl)-1,3-dithiolan-2-yl)benzoate (500 mg, 1.5 mmol, 1 eq) in DCM (5 mL). The mixture was stirred at 0 °C for 1 h, then diluted with DCM and passed through a short column packed with Al_2O_3/Mg_2SO_4 (20 g / 8 g). The collected DCM solution was concentrated, purified

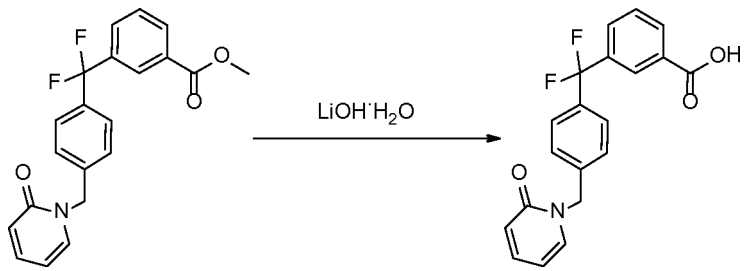
by prep-TLC (PE/EA = 15:1) to give methyl 3-(difluoro(p-tolyl)methyl)benzoate as a white oil (320 mg, 77%).



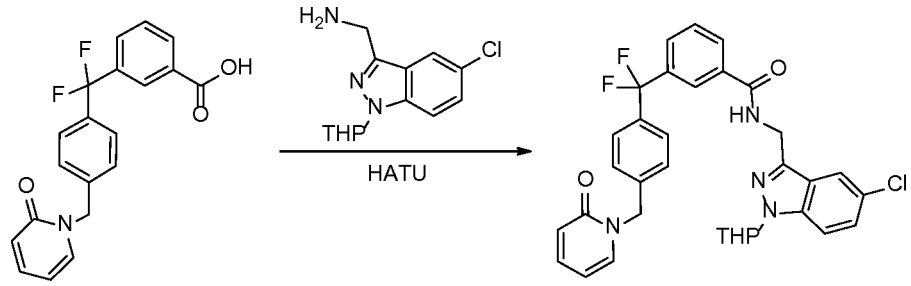
To a solution of methyl 3-(difluoro(p-tolyl)methyl)benzoate (276 mg, 1 mmol, 1 eq) in CCl_4 (10 mL) were added NBS (213 mg, 1.2 mmol, 1.2 eq) and AIBN (16.4 mg, 0.1 mmol, 0.1 eq). The mixture was stirred at 85 °C for 3 h, then concentrated, poured into water, and extracted with DCM (3x20 mL). The combined organic layers were concentrated, purified by prep-TLC (PE/EA = 15:1) to afford methyl 3-((4-(bromomethyl)phenyl)difluoromethyl)benzoate as a white oil (300 mg, 84.5%).



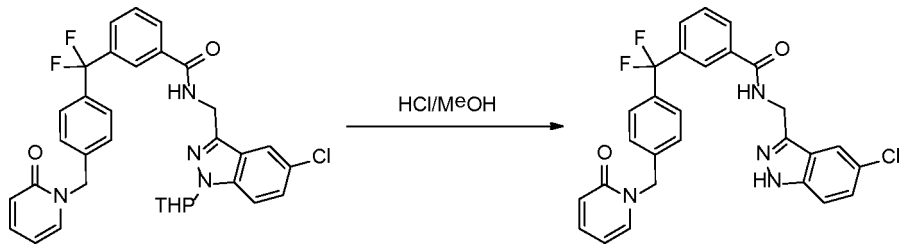
To a solution of methyl 3-((4-(bromomethyl)phenyl)difluoromethyl)benzoate (200 mg, 0.56 mmol, 1 eq) in MeCN (10 mL) were added pyridin-2(1H)-one (108 mg, 1.1 mmol, 2 eq) and K_2CO_3 (232 mg, 1.68 mmol, 3 eq). The mixture was stirred at 80 °C for 2 d, then concentrated, poured into water, and extracted with EA (3x20 mL). The combined organic layers were washed with brine, concentrated, and purified by prep-TLC (PE/EA = 1:1) to afford methyl 3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzoate as a white oil (90 mg, 43%).



To a solution of methyl 3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzoate (90 mg, 0.24 mmol, 1.0 eq) in THF/H_2O (15 mL/5 mL) was added LiOH.H_2O (101 mg, 2.4 mmol, 10.0 eq). The mixture was stirred at rt overnight, and concentrated to give 3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzoic acid (crude) for the next step.

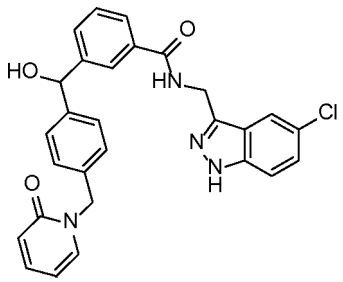


To a solution of 3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzoic acid (crude, ~0.24 mmol, 1 eq) in DMF (10 mL) were added TEA (48.5 mg, 0.48 mmol, 2 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (63.8 mg, 0.24 mmol, 1 eq) and HATU (182.4 mg, 0.48 mmol, 2 eq). The reaction mixture was stirred at rt for 3 h. The mixture was concentrated, and purified by prep-TLC (EA/Et_3N = 50/1) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide as a white oil (90 mg, 62%).

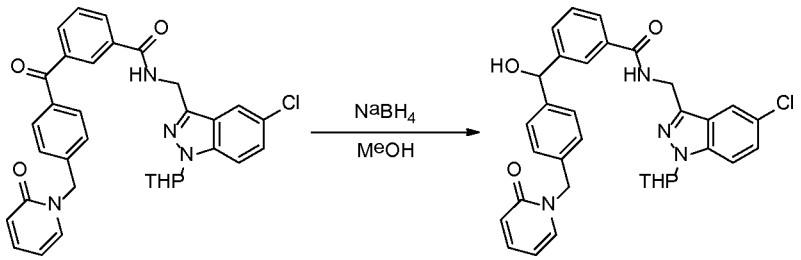


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide (90 mg, 0.15 mmol, 1.0 eq) in MeOH (4 mL) was added HCl/MeOH (4 mL). The mixture was stirred at rt for 12 h and then concentrated. The residue was purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide as a white solid (60 mg, 77%). LRMS ($M+H^+$) m/z caculated 519.1, found 518.8. ^1H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.95 (d, 1H), 7.88 (d, 1H), 7.70 (dd, 2H), 7.61-7.46 (m, 5H), 7.37 (m, 3H), 6.59 (d, 1H), 6.42 (q, 1H), 5.24 (s, 2H), 4.92 (s, 2H).

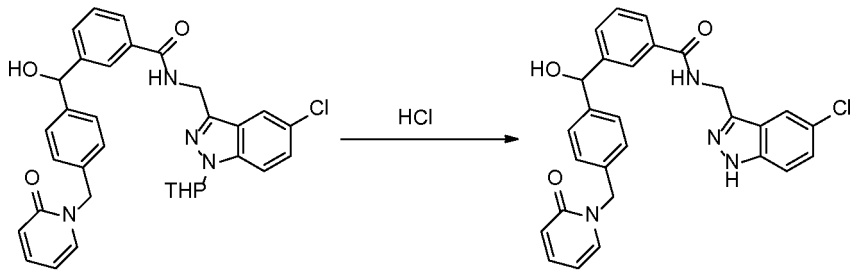
Example 55: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(hydroxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide



N-((5-chloro-1H-indazol-3-yl)methyl)-3-(hydroxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide

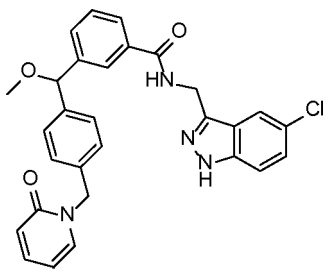


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzoyl)benzamide (30 mg, 0.1 mmol, 1.0 eq) in CH_3OH (5 mL) was added $NaBH_4$ (76 mg, 0.2 mmol, 2.0 eq) at 0 °C. The mixture was stirred at rt overnight, and then concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(hydroxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide as a yellow solid (30 mg, 50%).

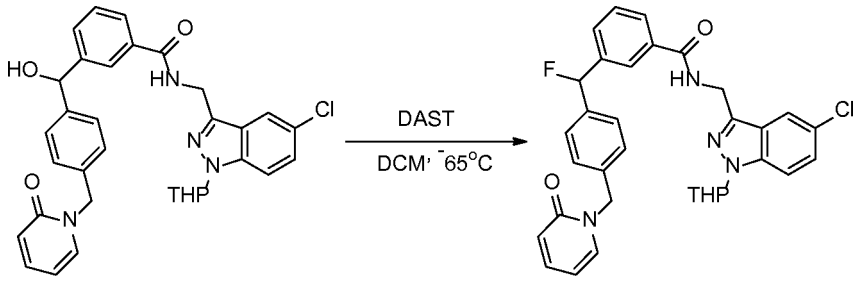


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(hydroxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide (30 mg, 0.051 mmol, 1.0 eq) in MeOH (5 mL) was added MeOH/HCl (4 N, 5 mL). The mixture was stirred at rt overnight and concentrated and purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-(hydroxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide HCl salt as a white solid (8.0 mg, 32%). LRMS ($M+H^+$) m/z caculated 499.2, found 499.1. ^1H NMR (CD_3OD, 400 MHz) δ 7.90(d, 2 H), 7.75 (m, 2 H), 7.60-7.48 (m, 3 H), 7.40-7.29 (dd, 4H), 7.28 (d, 2 H), 6.64 (d, 2 H), 6.49 (t, 1 H), 5.82 (s, 1H), 5.21 (s, 2 H), 4.92 (s, 2 H).

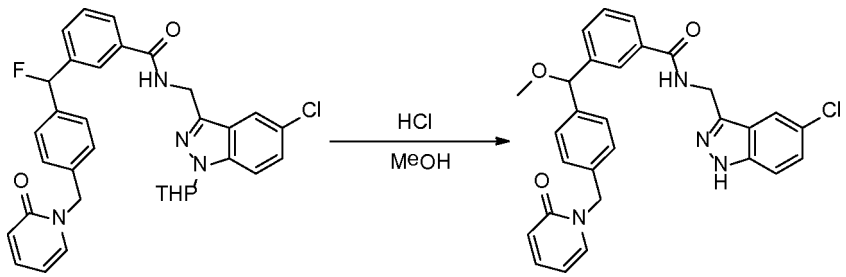
Example 56: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(methoxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide



N-((5-chloro-1*H*-indazol-3-yl)methyl)-3-(methoxy(4-((2-oxopyridin-1(2*H*)-yl)methyl)phenyl)methyl)benzamide

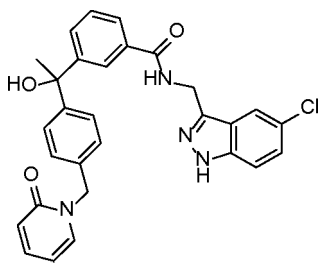


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(hydroxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide (29 mg, 0.05 mmol, 1.0 eq) in dry DCM under N_2 was added DAST (0.05 mL) dropwise at -65 °C. The mixture was stirred at -65 °C for 1 h. The reaction mixture was quenched with aqueous NH_4Cl, diluted with water, extracted with DCM (3x20 mL). The combined organic layers were concentrated, purified by prep-TLC (DCM/MeOH = 30/1) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(fluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide as a white solid (20 mg, 69%).

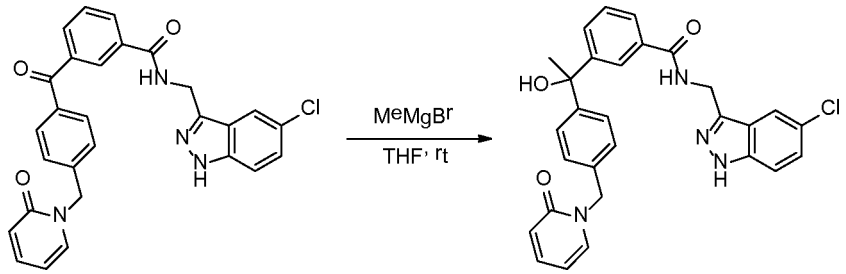


To a stirred suspension of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-3-(fluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide (20 mg, 0.034 mmol, 1.0 eq) in MeOH (2 mL) was added MeOH/HCl (4 N, 1 mL). The mixture was stirred at rt for 5 h. Then it was concentrated and rinsed with MeCN to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-(methoxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide HCl salt as a white solid (10 mg, 47%). LRMS ($M+H^+$) m/z caculated 513.2, found 513.1. ^1H NMR (CD_3OD, 400 MHz) δ 7.76 (s, 2 H), 7.56 (dd, 2 H), 7.40-7.35(m, 3 H), 7.29-7.21 (m, 4 H), 7.13 (m, 2 H), 6.44 (d, 1 H), 6.25 (t, 1 H), 5.21 (s, 1 H), 5.04 (s, 2 H) , 3.21 (s, 3 H).

Example 57: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(1-hydroxy-1-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)ethyl)benzamide

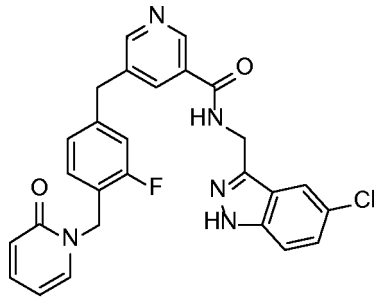


N-((5-chloro-1*H*-indazol-3-yl)methyl)-3-(1-hydroxy-1-(4-((2-oxopyridin-1(2*H*)-yl)methyl)phenyl)ethyl)benzamide

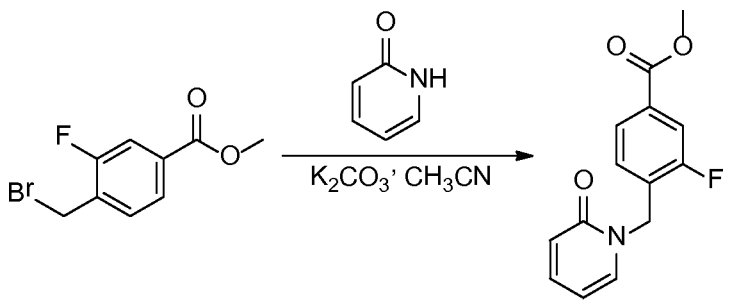


To a solution of N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzoyl)benzamide (30 mg, 0.060 mmol, 1 eq) in dry THF (3 mL) was added MeMgBr (3.0 M in THF, 0.12 mL) dropwise at 0 °C under N_2 and the mixture was stirred at rt overnight. The reaction mixture was quenched with aqueous NH_4Cl, diluted with water, extracted with EtOAc (3x20 mL). The combined organic layers was concentrated to afford N-((5-chloro-1H-indazol-3-yl)methyl)-3-(1-hydroxy-1-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)ethyl)benzamide as a white solid (9.5 mg, 30 %). LRMS ($M+H^+$) m/z caculated 513.2, found 513.2. ^1H NMR (CD_3OD, 400 MHz) δ7.90 (s, 1 H), 7.89 (d, 1 H), 7.69 (dd, 2 H), 7.59-7.48 (m, 3 H), 7.42-7.34 (m, 4H), 7.24 (d, 2 H), 6.57 (d, 1 H), 6.37 (t, 1 H), 5.17 (s, 2H), 4.91 (s, 2 H), 1.92 (s, 3 H).

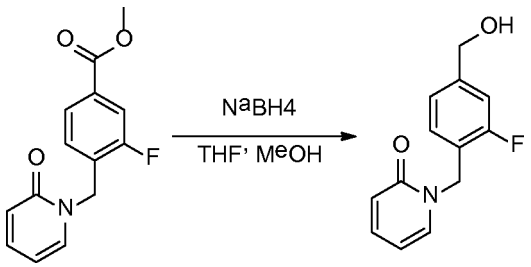
Example 58: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-fluoro-4-((2-oxopyridin-1 (2H)-yl)methyl)benzyl)nicotinamide



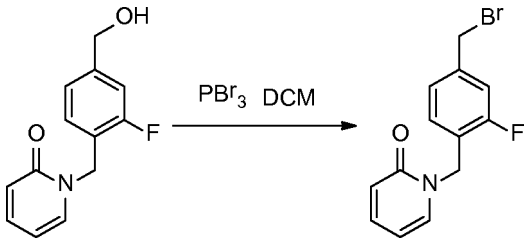
N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(3-fluoro-4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



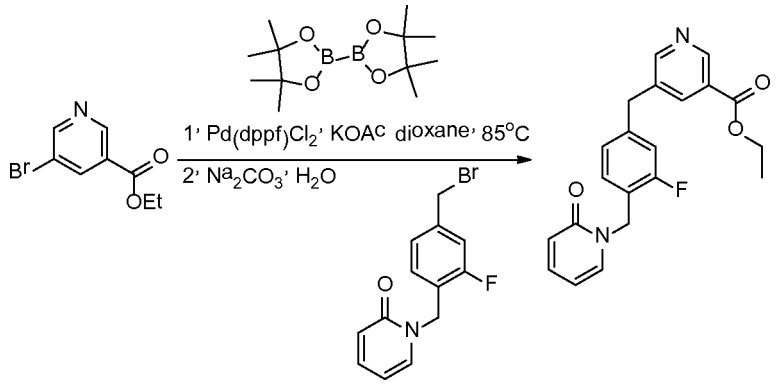
A mixture of methyl 4-(bromomethyl)-3-fluorobenzoate (500 mg, 2.02 mmol, 1.0 eq), pyridin-2(1H)-one (384 mg, 4.04 mmol, 2.0 eq) and K_2CO_3 (836 mg, 6.06 mmol, 3.0 eq) in MeCN (5 mL) was stirred at 85 °C overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified via flash chromatography to afford methyl 3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate as a yellow solid (430 mg, 82%).



To a solution of methyl 3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate (380 mg, 1.46 mmol, 1.0 eq) in THF (5 mL) was added $NaBH_4$ (332 mg, 8.74 mmol, 6.0 eq). The mixture was heated at 60 °C. The mixture was added dropwise MeOH (5 mL) over 1 h. The mixture was heated at 60 °C for 5 h. The mixture was added water (10 mL). The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to afford 1-(2-fluoro-4-(hydroxymethyl)benzyl)pyridin-2(1H)-one as a white solid (350 mg crude, quant).

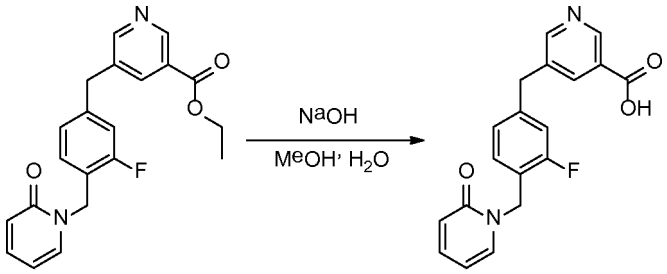


To a solution of 1-(2-fluoro-4-(hydroxymethyl)benzyl)pyridin-2(1H)-one (350 mg crude, 1.46 mmol, 1.0 eq) in DCM (5 mL) were added PBr_3 (593 mg, 2.19 mmol, 1.5 eq) at rt. The mixture was stirred at rt for 1 h. The mixture was mixed with saturated $NaHCO_3$ (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford 1-(4-(bromomethyl)-2-fluorobenzyl)pyridin-2(1H)-one as a white solid (170 mg, 39%).

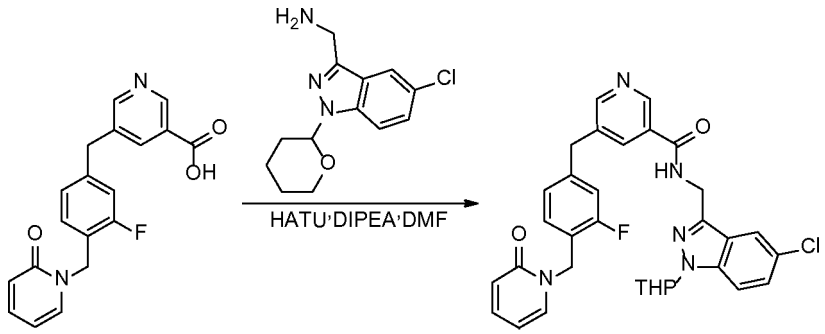


To a solution of ethyl 5-bromonicotinate (336 mg, 1.46 mmol, 1.0 eq) in 1,4-dioxane (10 mL) were added AcOK (420 mg, 4.38 mmol, 3.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (371 mg, 1.46 mmol, 1.0 eq) and $Pd(dppf)Cl_2$ (54 mg, 0.07 mmol, 0.05 eq). The mixture was heated at 85 °C overnight under N_2, and then the mixture was cooled to rt, to the mixture were added 1-(4-(bromomethyl)-2-fluorobenzyl)pyridin-2(1H)-one (432 mg, 1.46 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (54 mg, 0.07 mmol, 0.05 eq) and Na_2CO_3 (464 mg, 4.38 mmol, 3.0 eq) in water (5 mL). The mixture was heated to 95 °C for 2 h. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL) and extracted

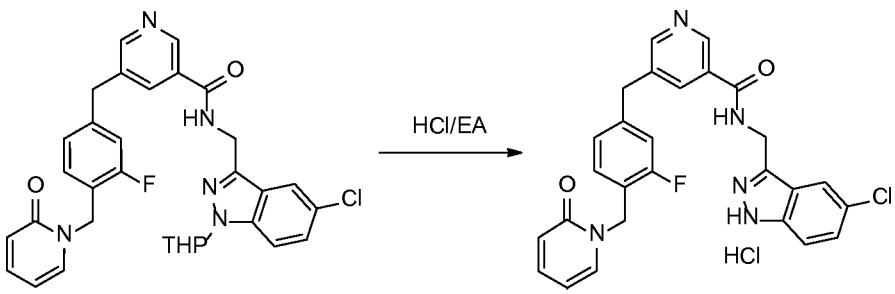
with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford ethyl 5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate as a white solid (100 mg, 48%).



To a solution of ethyl 5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate (100 mg, 0.27 mmol, 1.0 eq) in MeOH (2 mL) and H_2O (2 mL) was added NaOH (32 mg, 0.81 mmol, 3.0 eq). The mixture was heated at 60 °C for 30 min. The mixture was concentrated to remove MeOH, then diluted with ice-water (10 mL) and acidified with 1 N HCl to pH 2-3. The mixture was concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (10 mL) and filtered. The filtrate was concentrated under reduced pressure to afford 5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid as a yellow solid (150 mg crude, quant).

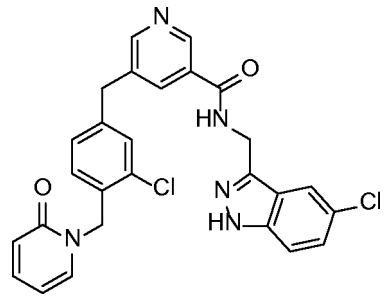


To a solution of 5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (150 mg crude, 0.27 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (104 mg, 0.81 mmol, 3.0 eq) and HATU (123 mg, 0.32 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (79 mg, 0.3 mmol, 1.1 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (120 mg, 76%).

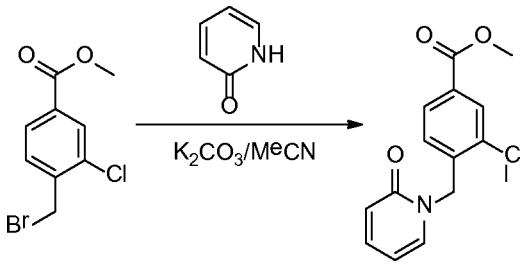


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (120 mg, 0.2 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/EA (2 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was filtered. The filtered cake was washed with Et_2O (10 mL). The filtered cake was dryness under reduced pressure to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide HCl salt as a white solid (70 mg, 65%). LRMS ($M+H^+$) m/z caculated 502.1, found 502.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.16 (brs, 1 H), 9.66 (t, 1 H), 9.13 (s, 1 H), 8.93 (s, 1 H), 8.66 (s, 1 H), 7.94 (d, 1 H), 7.71 (dd, 1 H), 7.54 (d, 1 H), 7.50-7.40 (m, 1 H), 7.34 (dd, 1 H), 7.24 (d, 1 H), 7.14 (d, 1 H), 7.08 (t, 1 H), 6.39 (d, 1 H), 6.24 (t, 1 H), 5.07 (s, 2 H), 4.81 (d, 2 H), 4.16 (s, 2 H).

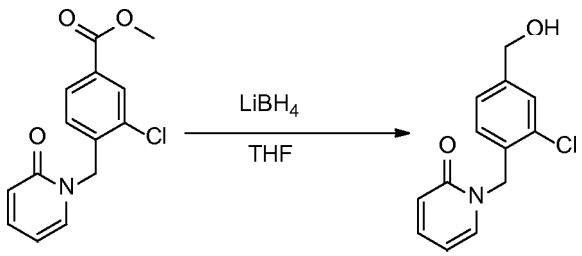
Example 59: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-chloro-4-((2-oxopyridin-1 (2H)-yl)methyl)benzyl)nicotinamide



N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

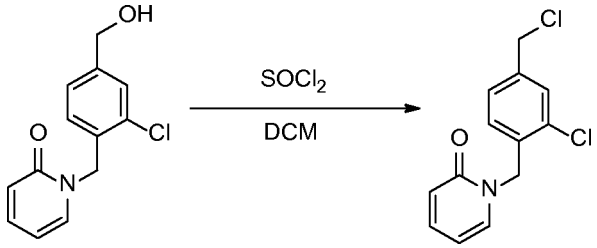


To a suspension of methyl 4-(bromomethyl)-3-chlorobenzoate (500 mg, 1.8 mmol, 1.0 eq) and pyridin-2(1H)-one (360 mg, 3.8 mmol, 2.0 eq) in MeCN (10 mL) was added K_2CO_3 (523 mg, 3.8 mmol, 2.0 eq). The mixture was heated to 85 °C overnight. After cooled to rt, the mixture was concentrated in vacuo to give a solid, whihc was purified by flash chromatography to afford methyl 3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate as a white solid (413 mg, 78%).

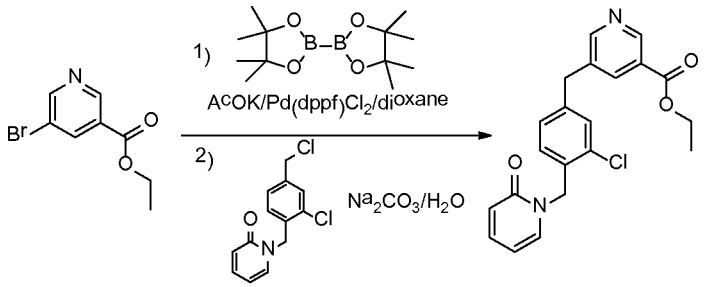


To a solution of methyl 3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate (410 mg, 1.4 mmol, 1.0 eq) in THF (20 mL) was added $LiBH_4$ (325 mg, 14 mmol, 10.0 eq) carefully. After addition, the mixture was heated to reflux for 1 h and allowed to cool. The mixture was quenched with water (20 mL), extracted with EA (20

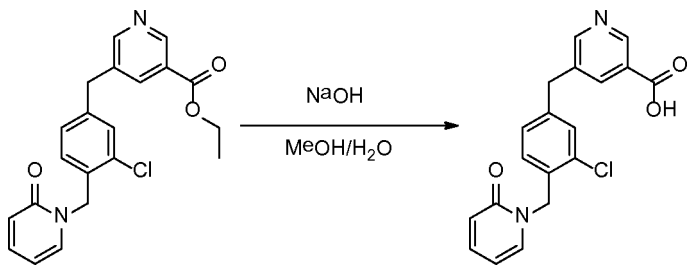
mL x 3), the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 1-(2-chloro-4-(hydroxymethyl)benzyl)pyridin-2(1H)-one as a yellow oil (352 mg, 95%).



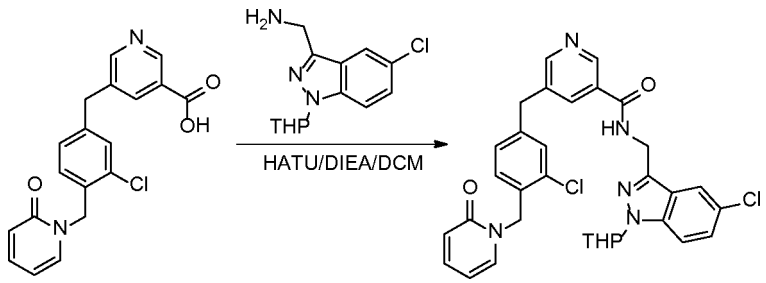
To a solution of 1-(2-chloro-4-(hydroxymethyl)benzyl)pyridin-2(1H)-one (350 mg, 1.4 mmol, 1.0 eq) in DCM (10 mL) was added drop wise $SOCl_2$ (1 mL) in ice-water bath. After addition, the mixture was stirred at rt for 1 h. After removal of the solvent, the residue was purified by flash chromatography to afford 1-(2-chloro-4-(chloromethyl)benzyl)pyridin-2(1H)-one as a white solid (360 mg, 96%).



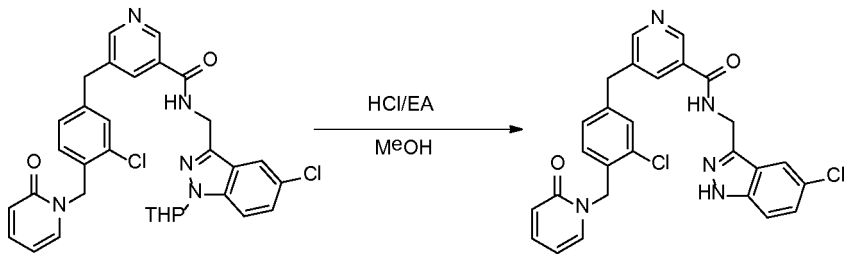
To a suspension of ethyl 5-bromonicotinate (1.0 g, 4.3 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1 g, 4.3 mmol, 1.0 eq) and AcOK (1.280 g, 13 mmol, 3.0 eq) in dioxane (50 mL) was added Pd(dppf)Cl_2 (160 mg, 0.21 mmol, 0.05 eq). The mixture was heated to 85 °C under N_2 overnight. After cooled to rt, 1-(2-chloro-4-(chloromethyl)benzyl)pyridin-2(1H)-one (360 mg, 1.3 mmol, 0.3 eq), and a solution of Na_2CO_3 (1.380 g, 13 mmol, 3 eq) in water (8 mL) were added, followed by Pd(dppf)Cl_2 (160 mg, 0.21 mmol, 0.05 eq). The mixture was then heated to 95 °C for a further 2 h and allowed to cool. After removal of the solvent, the residue was quenched with water (30 mL), extracted with EA (3x30 mL), the combined organic layer was washed with brine dried over Na_2SO_4, filtered and concentrated in vacuo to give an oil, which was further purified by chromatography on silica gel column, elution with DCM/MeOH (30/1 to 10/1) to afford ethyl 5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate as a yellow solid (399 mg, crude).



To a solution of ethyl 5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate (399 mg, crude, 1.0 eq) in MeOH (10 mL) and H_2O (10 mL) was added NaOH (400 mg, 10.0 mmol). The mixture was stirred at 75 °C for 2 h. The organic solvents were evaporated. To the residue was added conc. HCl till pH 3. The precipitate was filtered and dried to afford 5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid as a white solid (260 mg, 54% of above two steps).

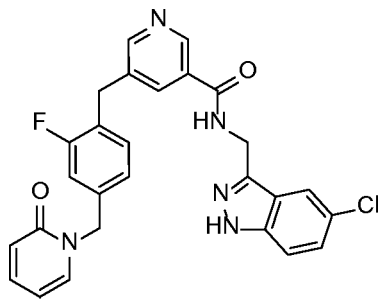


A mixture of 5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (260 mg, 0.73 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (195 mg, 0.73 mmol, 1.0 eq), HATU (279 mg, 0.73 mmol, 1.0 eq) and DIEA (1 mL) in DCM (20 mL) was stirred at rt for 2 h, the mixture was diluted with DCM (50 mL), washed with saturated $NaHCO_3$ (25 mL), brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was then further purified by flash chromatography (MeCN/H_2O = 25%- 95%) to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (316 mg, 71%).

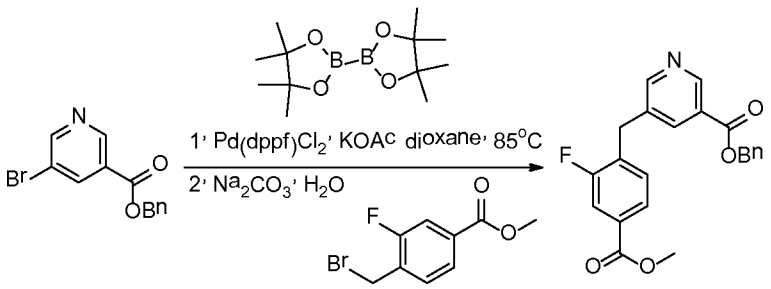


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (310 mg, 0.51 mmol, 1.0 eq) in MeOH (5 mL) and HCl/EA (3 N, 10 mL) was stirred at rt for 20 h. Then the mixture was concentrated. The residue was purified by flash chromatography (MeCN/H_2O = 25%- 95%) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (76 mg, 26%). LRMS ($M+H^+$) m/z calculated 518.1, found 518.1. ^1H NMR (DMSO-*d6*, 300 MHz) δ 13.07 (s, 1H), 9.28 (t, 1H), 8.87 (d, 1H), 8.64 (d, 1H), 8.06 (t, 1H), 7.90 (d, 1H), 7.65 (m, 1H), 7.54-7.43 (m, 3H) , 7.33 (m, 1H), 7.21 (m, 1H), 6.81 (d, 1H), 6.42 (d, 1H), 6.25 (m, 1H), 5.10 (s, 2H), 4.78 (d, 2H), 4.01 (s, 2H).

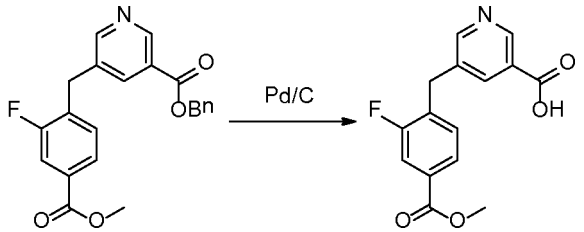
Example 60: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2-fluoro-4-((2-oxopyridin-1 (2H)-yl)methyl)benzyl)nicotinamide



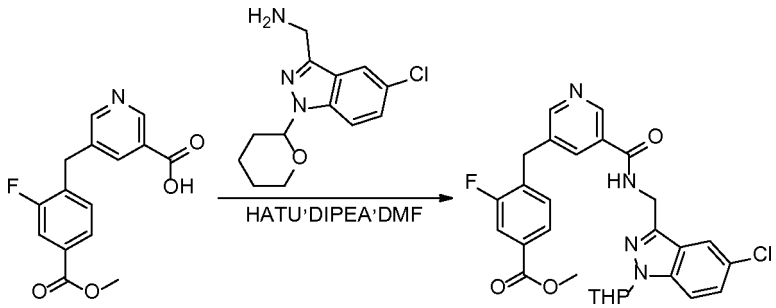
N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(2-fluoro-4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



To a solution of benzyl 5-bromonicotinate (1.0 g, 3.42 mmol, 1.0 eq) in 1,4-dioxane (10 mL) were added AcOK (985 mg, 10.26 mmol, 3.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (870 mg, 3.42 mmol, 1.0 eq) and $Pd(dppf)Cl_2$ (125 mg, 0.17 mmol, 0.05 eq). The mixture was heated at 85 °C overnight under N_2, and then the mixture was cooled to rt, to the mixture were added methyl 4-(bromomethyl)-3-fluorobenzoate (845 mg, 3.42 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (125 mg, 0.17 mmol, 0.05 eq) and Na_2CO_3 (1.09 g, 10.26 mmol, 3.0 eq) in water (5 mL). The mixture was heated to 95 °C for 2 h. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford benzyl 5-(2-fluoro-4-(methoxycarbonyl)benzyl)nicotinate as a yellow oil (360 mg, 28%).

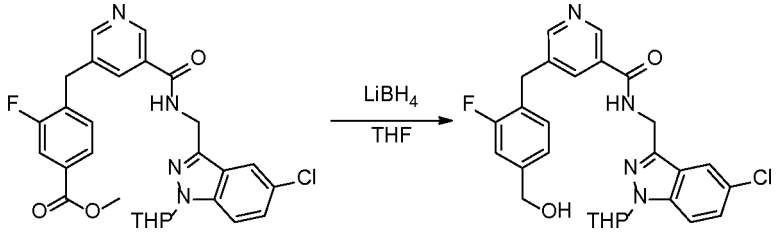


To a solution of benzyl 5-(2-fluoro-4-(methoxycarbonyl)benzyl)nicotinate (360 mg, 0.95 mmol, 1.0 eq) in MeOH (5 mL) was added Pd/C (36 mg, 10% Pd). The mixture was hydrogenated at rt overnight. The mixture was filtered and the filtered cake was washed with DCM (10 mL) and MeOH (10 mL). The filtrate was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford 5-(2-fluoro-4-(methoxycarbonyl)benzyl)nicotinic acid as a white solid (278 mg crude, quant).

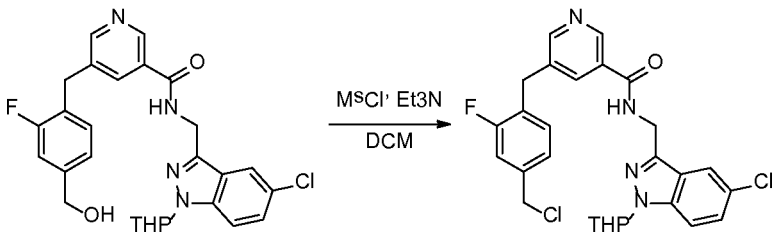


To a solution of 5-(2-fluoro-4-(methoxycarbonyl)benzyl)nicotinic acid (278 mg crude, 0.95 mmol, 1.0 eq) in DMF (5 mL) were added DIPEA (368 mg, 2.85 mmol, 3.0 eq) and HATU (433 mg, 1.14 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (278 mg, 1.05 mmol, 1.1 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was

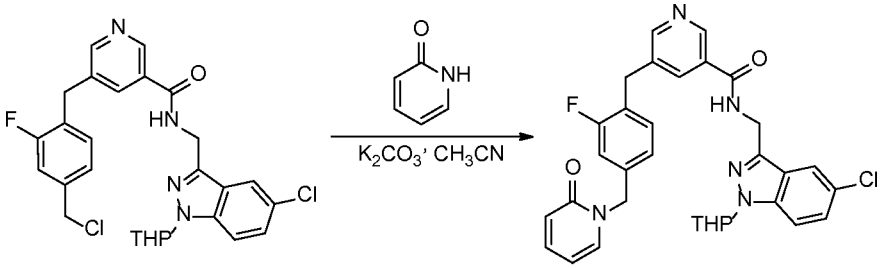
purified via flash chromatography to afford methyl 4-((5-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl) methyl)carbamoyl)pyridin-3-yl)methyl)-3-fluorobenzoate as an off-white solid (360 mg, 71%).



To a solution of methyl 4-((5-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-3-fluorobenzoate (360 mg, 0.67 mmol, 1.0 eq) in THF (10 mL) was added $LiBH_4$ (147 mg, 6.7 mmol, 10.0 eq). The mixture was heated at 60 °C overnight. The mixture was added water (5 mL). The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl) methyl)-5-(2-fluoro-4-(hydroxymethyl)benzyl)nicotinamide as a yellow solid (160 mg, 47%).

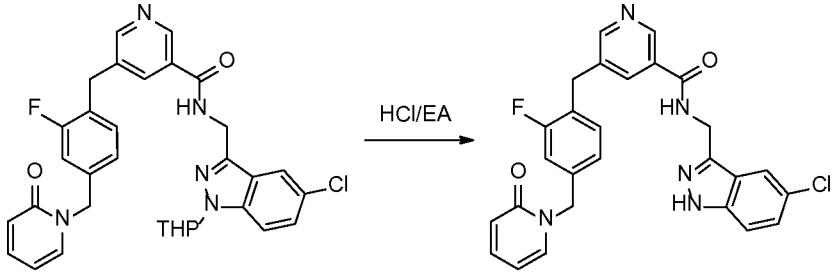


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(2-fluoro-4-(hydroxymethyl)benzyl)nicotinamide (140 mg, 0.28 mmol, 1.0 eq) in DCM (2 mL) were added Et_3N (28 mg, 0.28 mmol, 1.0 eq) and MsCl (32 mg, 0.28 mmol, 1.0 eq) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl) methyl)-5-(4-(chloromethyl)-2-fluorobenzyl)nicotinamide as a white solid (25 mg, 17%).



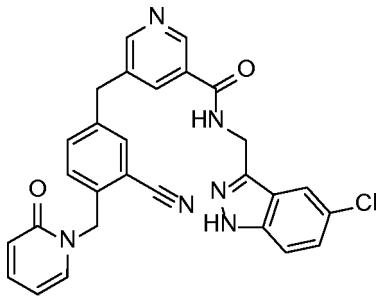
A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(chloromethyl)-2-fluorobenzyl)nicotinamide (20 mg, 0.038 mmol, 1.0 eq), pyridin-2(1H)-one (18 mg, 0.19 mmol, 5.0 eq) and K_2CO_3 (16 mg, 0.11 mmol, 3.0 eq) in MeCN (2 mL) was stirred at 80 °C overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-

(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow solid (13 mg, 46%).

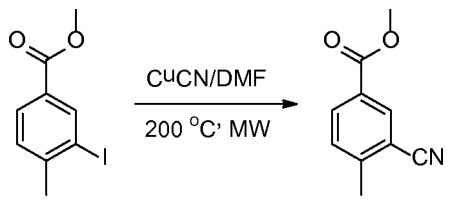


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (13 mg, 0.022 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/EA (2 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was added saturated $NaHCO_3$ (10 mL) and concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (10 mL), filtered. The filtrate was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2-fluoro-4-((2-oxopyridin-1(2H)-yl) methyl)benzyl)nicotinamide as a white solid (7 mg, 64%). LRMS ($M+H^+$) m/z caculated 502.1, found 502.1. ^1H NMR (CD_3OD-d_4, 400 MHz) δ 8.72 (d, 1 H), 8.45 (s, 1 H), 7.97 (s, 1 H), 7.75 (d, 1 H), 7.59 (dd, 1 H), 7.46-7.40 (m, 1 H), 7.38 (d, 1 H), 7.24 (dd, 1 H), 7.17 (t, 1 H), 6.96 (t, 2 H), 6.46 (d, 1 H), 6.29 (td, 1 H), 5.05 (s, 2 H), 4.79 (s, 2 H), 3.97 (s, 2 H).

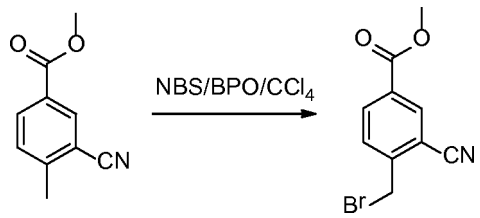
Example 61: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



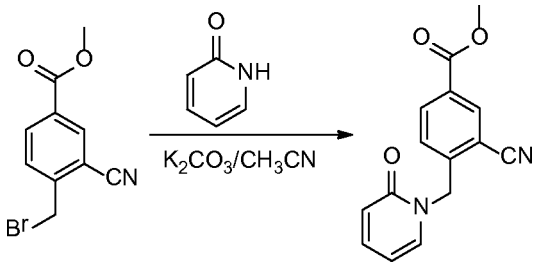
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



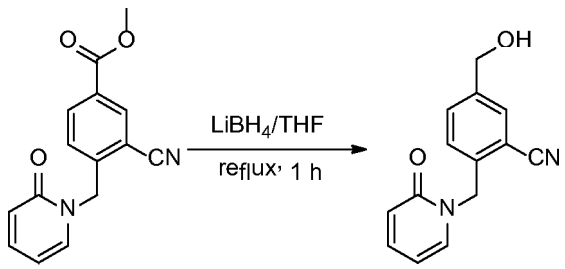
A mixture of methyl 3-iodo-4-methylbenzoate (2 g, 7.2 mmol, 1.0 eq) and CuCN (774 mg, 8.6 mmol, 1.2 eq) in NMP (20 mL) was stirred at 200 °C wiht microwave for 1 h. Then the mixture was poured into water (50 mL), extracted with EtOAc (50 mL x3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (PE/EtOAc = 5/1) to afford methyl 3-cyano-4-methylbenzoate as a white solid (1.2 g, 95%).



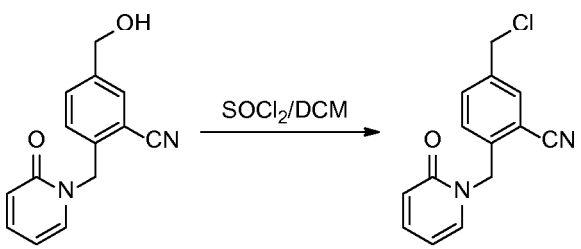
A mixture of methyl 3-cyano-4-methylbenzoate (1.7 g, 9.7 mmol, 1.0 eq), NBS (2.07 g, 11.6 mmol, 1.2 eq) and BPO (234 mg, 0.97 mmol, 0.1 eq) in CCl_4 (20 mL) was stirred at 90 °C under N_2 overnight. Then the reaction was quenched with water (10 mL), extracted with DCM (50 mL x3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (PE/EtOAc = 20/1) to afford methyl 4-(bromomethyl)-3-cyanobenzoate as a yellow solid (1.5 g, 61%).



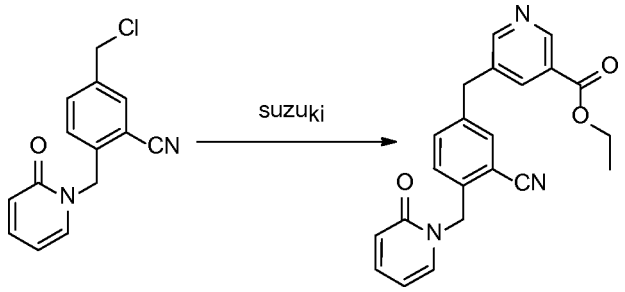
A mixture of methyl 4-(bromomethyl)-3-cyanobenzoate (1.5 g, 5.9 mmol, 1.0 eq), pyridin-2(1H)-one (842 mg, 8.9 mmol, 1.5 eq) and K_2CO_3 (1.63 g, 11.8 mmol, 2.0 eq) in CH_3CN (30 mL) was stirred at 85 °C overnight. After cooled to rt, the mixture was filtered. The filtrate was concentrated. The residue was purified on silica gel column (PE/EtOAc = 1/1) to afford methyl 3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate as a yellow solid (1.2 g, 75%).



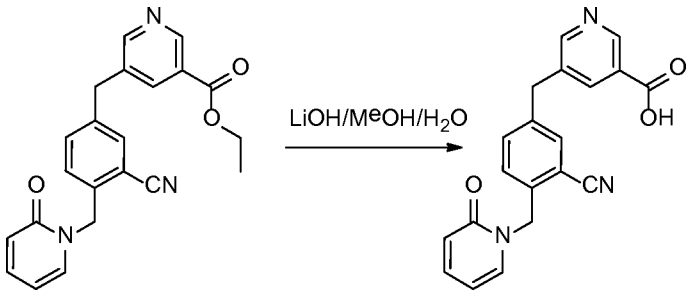
To a solution of methyl 3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate (1 g, 3.7 mmol, 1.0 eq) in THF (30 mL) was added $LiBH_4$ (810 mg, 37 mmol, 10.0 eq). The mixture was refluxed and stirred for 1 h. LCMS showed the reaction complete. Then the mixture was cooled to rt and dropped to water. The obtained mixture was extracted with EtOAc (50 mL ×3). The mixture was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (PE/EtOAc = 1/2) to give 5-(hydroxymethyl)-2-((2-oxopyridin-1(2H)-yl)methyl)benzonitrile as a yellow oil (720 mg, 81%).



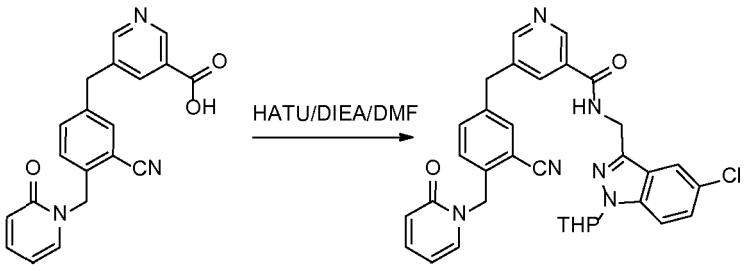
The mixture of 5-(hydroxymethyl)-2-((2-oxopyridin-1(2H)-yl)methyl)benzonitrile (620 mg, 2.58 mmol, 1.0 eq) in DCM (5 mL) and $SOCl_2$ (5 mL) was stirred at rt overnight. Then the mixture was concentrated. The residue was purified on silica gel column (PE/EtOAc = 5/1) to give 5-(chloromethyl)-2-((2-oxopyridin-1(2H)-yl)methyl)benzonitrile as a yellow oil (420 mg, 63%).



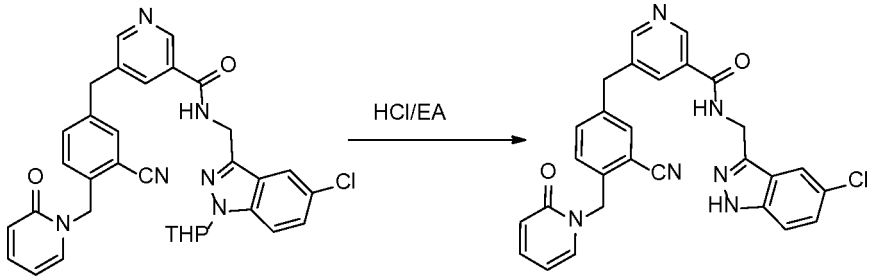
The mixture of ethyl 5-bromonicotinate (374 mg, 1.6 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (406 mg, 1.6 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (58 mg, 0.05 eq) and KOAc (470 mg, 4.8 mmol, 3.0 eq) in dioxane (15 mL) was degassed with N_2 and stirred at 85 °C overnight. Then the mixture was cooled, 5-(chloromethyl)-2-((2-oxopyridin-1(2H)-yl)methyl)benzonitrile (420 mg, 1.6 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (58 mg, 0.05 eq) and an aqueous solution of Na_2CO_3 (509 mg, 4.8 mmol, 3.0 eq) in 8 mL of water were added. The mixture was degassed with N_2 and stirred at 95 °C overnight. Then the mixture was cooled and concentrated, the residue was dissolved in EtOAc (150 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via silica gel column (DCM/EtOAc = 1/1) to afford ethyl 5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate as a yellow solid (410 mg, 69%).



The solution of ethyl 5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate (410 mg, 1.1 mmol, 1.0 eq) in MeOH (10 mL) was treated with an aqueous solution of LiOH (92 mg, 2.2 mmol, 2.0 eq) in 5 mL of water. The mixture was stirred for 2 h at rt. Then the mixture was concentrated and the residue was acidified with 1 N HCl till pH 3. The mixture was concentrated to give 5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid as a yellow solid (520 mg, quant). The solid was used for the next step without further purification.

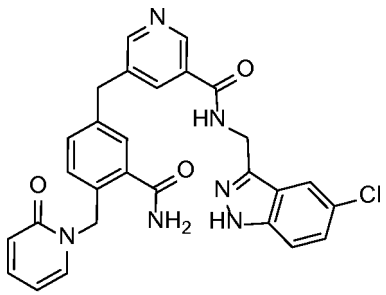


A mixture of (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (292 mg, 1.1 mmol, 1.0 eq), 5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (380 mg, 1.1 mmol, 1.0 eq), HATU (627 mg, 1.65 mmol, 1.5 eq) and DIEA (426 mg, 3.3 mmol, 3.0 eq) in DMF (20 mL) was stirred at rt for 2 h. The mixture was poured into water (50 mL). The appeared solid was filtered and dried to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a brown solid (550 mg, 84%). The solid was used for the next step without further purification.

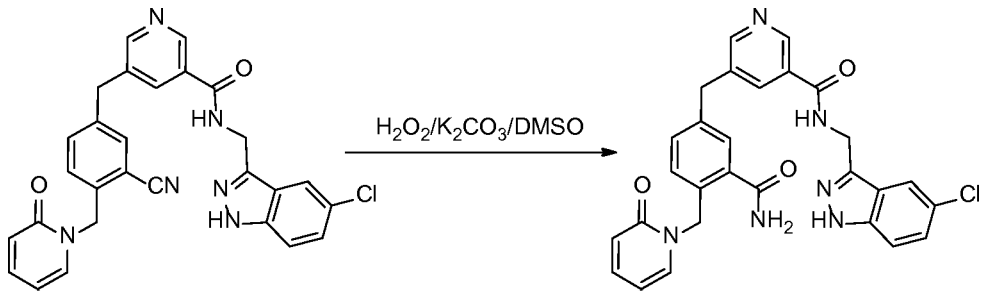


The solutuion of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (550 mg, 0.93 mmol, 1.0 eq) in 1 N HCl/EtOAc was stirred at rt overnight. Then the mixture was concentrated and the residue was washed with MeOH to give N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide HCl salt as a white solid (382 mg, 81%). LRMS ($M+H^+$) m/z calculated 509.1, found 509.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.20 (d, 1H), 8.95 (s, 1H), 8.91 (s, 1H), 7.92 (s, 1H), 7.85 (dd, 1H), 7.79 (d, 1H), 7.67-7.61 (m, 2H), 7.52 (d, 2H), 7.39 (dd, 1H), 7.28 (d, 1H), 6.62 (d, 1H), 6.54 (t, 1H), 5.41 (s, 2H), 4.97 (s, 2H), 4.36 (s, 2H).

Example 62: Preparation of 5-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro- 1H-indazol-3-yl)methyl)nicotinamide



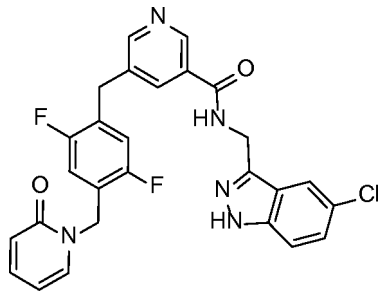
5-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide



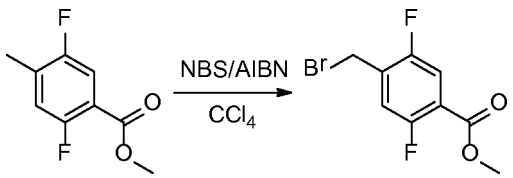
A mixture of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (150 mg, 0.3 mmol, 1.0 eq) and K_2CO_3 (41 mg, 0.3 mmol, 1.0 eq) in DMSO

(3 mL) was added H_2O_2 (3 mL) dropwise. Then the mixture was stirred at rt for 3 h. Then the mixture was poured into water (10 mL). The appeared solid was filtered and purified by flash chromatography to afford 5-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide as a white solid (20 mg, 13%). LRMS ($M+H^+$) m/z calculated 527.2, found 527.2. ^{1}H NMR (DMSO-d6, 300 MHz) δ 13.08 (s, 1H), 9.27 (t, 1H), 8.86 (d, 1H), 8.63 (d, 1H), 8.07-8.06 (m, 1H), 7.90 (d, 1H), 7.72 (dd, 1H), 7.54-7.51 (m, 2H), 7.46-7.41 (m, 2H), 7.35-7.26 (m, 2H), 6.88 (d, 1H), 6.39 (d, 1H), 6.22 (t, 1H), 5.21 (s, 2H), 4.78 (d, 2H), 4.01 (s, 2H).

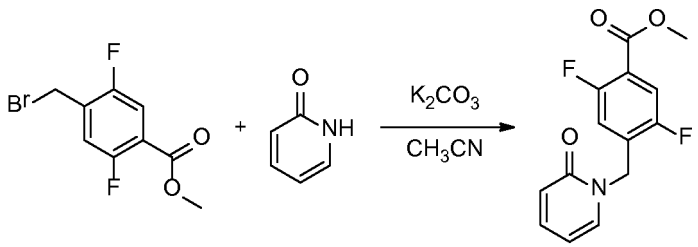
Example 63: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2,5-difluoro-4-((2- oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



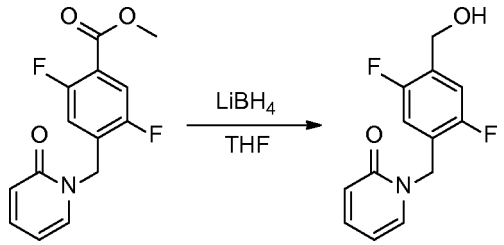
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



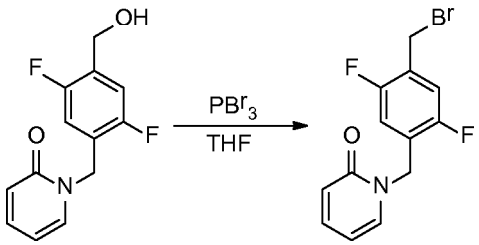
To a solution of methyl 2,5-difluoro-4-methylbenzoate (500 mg, 2.69 mmol, 1.0 eq) in CCl_4 (6 mL) were added NBS (527 mg, 2.96 mmol, 1.1 eq), AIBN (13 mg, 0.08 mmol). The mixture was stirred at 85 °C overnight. Then the mixture was evaporated to dryness, and the residue was purified via silica column (PE/EtOAc=100/1) to afford methyl 4-(bromomethyl)-2,5-difluorobenzoate as a white solid (190 mg, 27%).



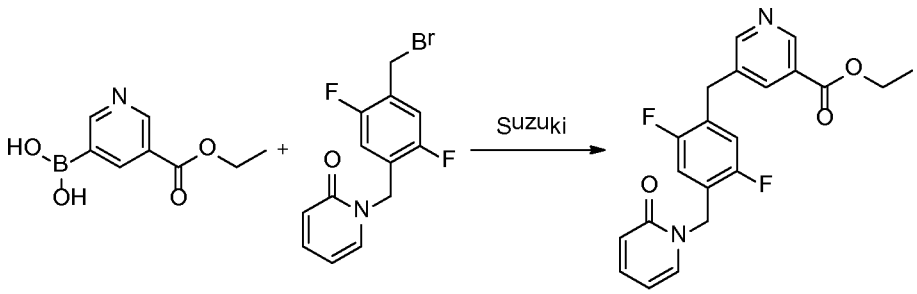
To a solution of methyl 4-(bromomethyl)-2,5-difluorobenzoate (500 mg, 2.0 mmol, 1.0 eq), pyridin-2(1H)-one (232 mg, 2.44 mmol) in CH_3CN (10 mL) was added K_2CO_3 (841 mg, 6.1 mmol, 3.0 eq). The mixture was stirred at 70 °C for 2 h. The mixture was evaporated to dryness, the residue was purified via silica column (PE/EtOAc = 1/1) to afford methyl 2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate as a white solid (528 mg, 78%).



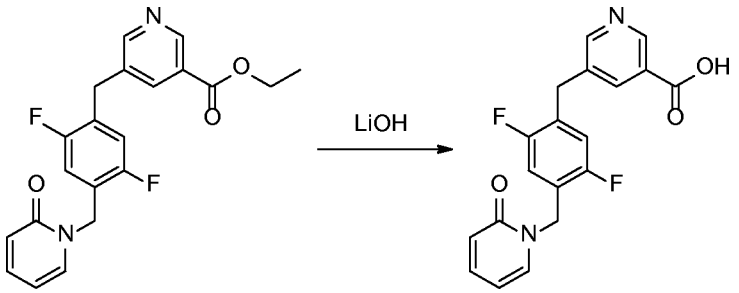
To a solution of methyl 2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate (400 mg, 1.43 mmol, 1.0 eq) in THF (30 mL) was added $LiBH_4$ (157 mg, 7.17 mmol, 5.0 eq). The mixture was stirred at 70 °C for 2 h. After cooling to rt, 20 mL of H_2O was added into the mixture, and the mixture was extracted with EA (3x30 mL). The organic extracts were concentrated to afford 1-(2,5-difluoro-4-(hydroxymethyl)benzyl)pyridin-2(1H)-one as a yellow solid (300 mg, 83%).



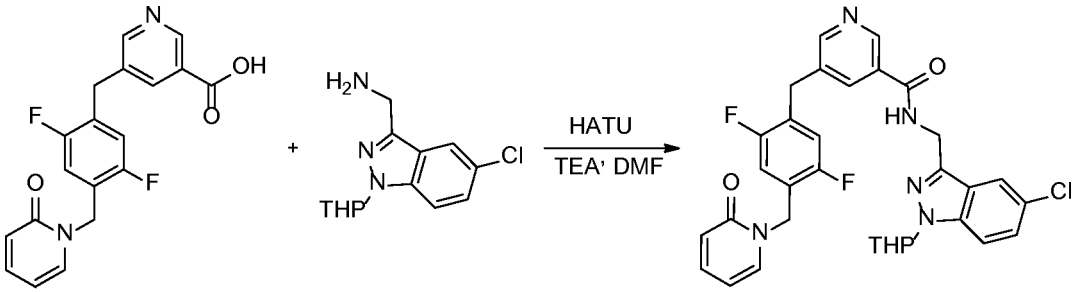
To a solution of 1-(2,5-difluoro-4-(hydroxymethyl)benzyl)pyridin-2(1H)-one (300 mg, 1.19 mmol, 1.0 eq) in THF (5 mL) was added PBr_3 (355 mg, 1.31 mmol, 1.1 eq) at 0 °C. The mixture was stirred at 0 °C for 2 h. 10 mL of H_2O was added into the mixture, and the mixture was extracted with EA (3x15 mL). The organic extracts were concentrated to afford 1-(4-(bromomethyl)-2,5-difluorobenzyl)pyridin-2(1H)-one as a yellow solid (350 mg, 94%).



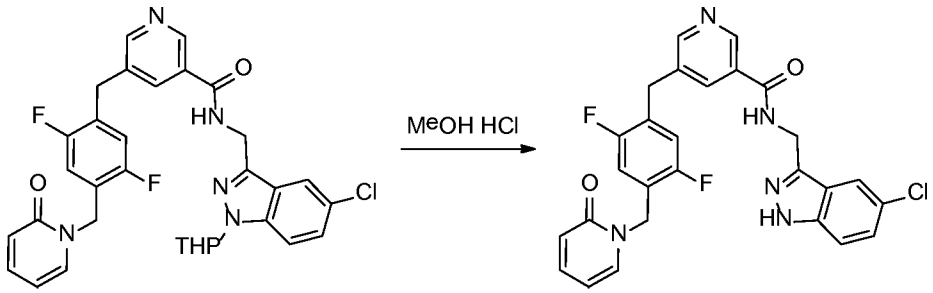
The mixture of (5-(ethoxycarbonyl)pyridin-3-yl)boronic acid (195 mg, 1.0 mmol, 1.0 eq), 1-(4-(bromomethyl)-2,5-difluorobenzyl)pyridin-2(1H)-one (314 mg, 1.0 mmol, 1.0 eq), $Pd(Ph_3P)_4$ (115 mg, 0.1 eq) and Na_2CO_3 (318 mg, 3.0 mmol, 3.0 eq) in dioxane (10 mL) and H_2O (1.0 mL) was degassed with N_2 and stirred at 85 °C overnight. After cooling to rt, the mixture was concentrated. The residue was diluted with EtOAc (100 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via silica column (PE/EtOAc = 1/4) to afford ethyl 5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate as a yellow solid (120 mg, 31%).



To a solution of ethyl 5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate (120 mg, 0.31 mmol, 1.0 eq) in THF (6 mL) and H_2O (2 mL) was added LiOH.H_2O (131 mg, 3.1 mmol, 10.0 eq). The mixture was stirred at rt overnight. The mixture was evaporated to dryness to afford 5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid as a yellow solid (111 mg, quant), which was used in the next step directly.



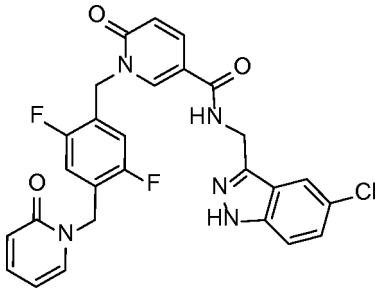
A mixture of 5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (111 mg, 0.31 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (83 mg, 0.31 mmol, 1.0 eq), HATU (177 mg, 0.47 mmol, 1.5 eq) and TEA (94 mg, 0.93 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt overnight. The mixture was purified directly by flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow oil (85 mg, 45%).



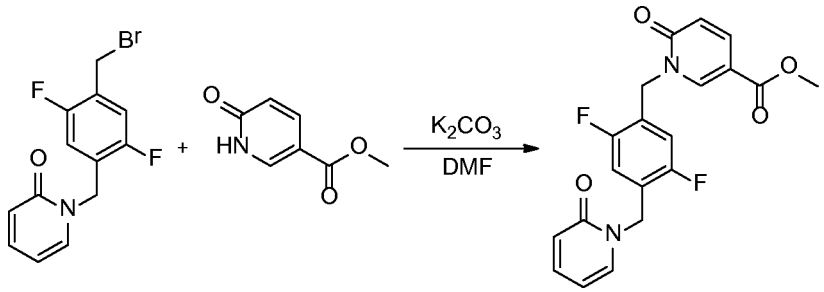
A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (85 mg, 0.17 mmol, 1.0 eq) in HCl/MeOH (25% w/w, 6 mL) was stirred at rt for 2 h. The mixture was purified directly by flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (25 mg, 35%). LRMS ($M+H^+$) m/z calculated 520.13, found 520.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.20 (s, 1H), 8.95 (s, 1H), 8.91 (s, 1H), 7.91 (s, 1H), 7.85 (d, 1H), 7.67 (t, 1H), 7.52 (d, 1H), 7.38 (d, 1H), 7.28 (t, 1H), 7.11 (t, 1H), 6.64 (d, 1H), 6.54 (t, 1H), 5.25 (s, 2H), 4.96 (s, 2H), 4.32 (s, 2H).

Example 64: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-1-(2,5-difluoro-4-((2- oxopyridin-1(2H)-

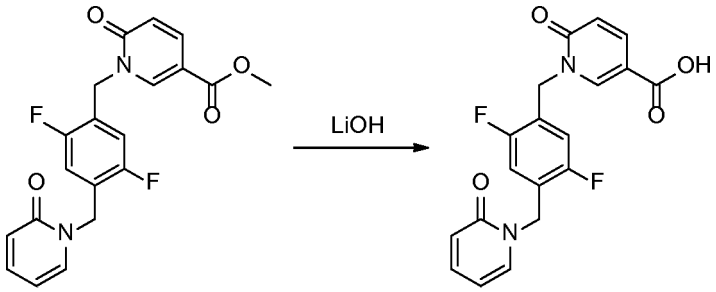
yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



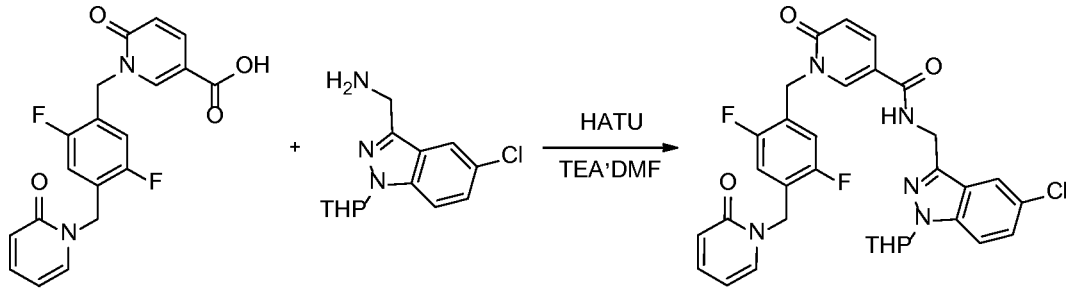
N-((5-chloro-1*H*-indazol-3-yl)methyl)-1-(2,5-difluoro-4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



To a solution of 1-(4-(bromomethyl)-2,5-difluorobenzyl)pyridin-2(1H)-one (200 mg, 0.63 mmol, 1.0 eq), methyl 6-oxo-1,6-dihydropyridine-3-carboxylate (97 mg, 0.63 mmol) in DMF (5 mL) was added K_2CO_3 (264 mg, 1.91 mmol, 3.0 eq). The mixture was stirred at RT overnight. The mixture was evaporated to dryness, the residue was purified via silica column (PE/EtOAc = 1/1) to afford methyl 1-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate as a yellow oil (170 mg, 62%).

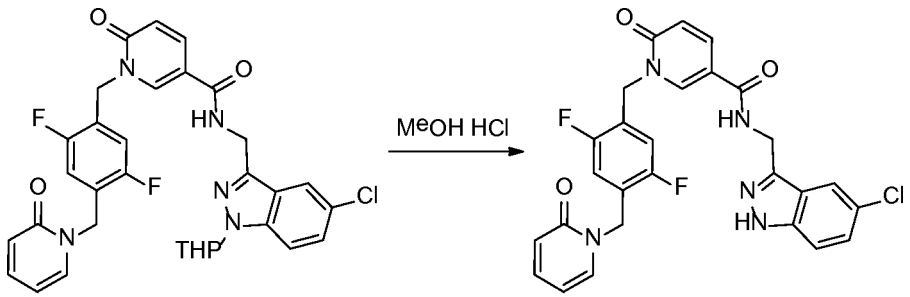


To a solution of methyl 1-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (170 mg, 0.44 mmol, 1.0 eq) in THF (6 mL) and H_2O (2 mL) was added LiOH.H_2O (184 mg, 4.4 mmol, 10.0 eq). The mixture was stirred at rt overnight. The mixture was evaporated to dryness to afford 1-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid as a white solid (164 mg, quant), which was used in the next step directly.



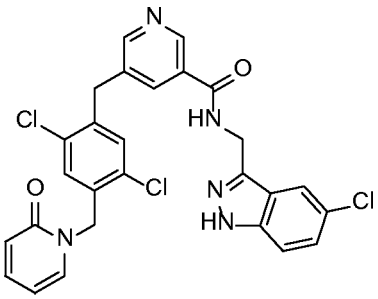
A mixture of 1-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (164 mg, 0.44 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-

yl)methanamine (129 mg, 0.48 mmol, 1.0 eq), HATU (251 mg, 0.66 mmol, 1.5 eq) and TEA (133 mg, 1.32 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt overnight. The mixture was purified directly by flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide as a colorless oil (70 mg, 26%).

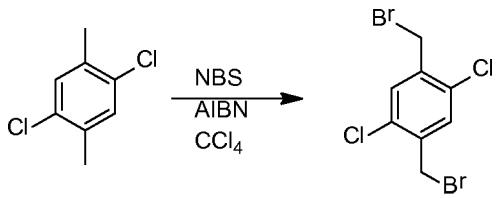


A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (70 mg, 0.11 mmol, 1.0 eq) in HCl/MeOH (25% w/w, 6 mL) was stirred at rt for 2 h. The mixture was purified directly by flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-1-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide as a white solid (15 mg, 25%). LRMS ($M+H^+$) m/z calculated 536.12, found 536.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.31 (s, 1H), 7.84-7.86 (m, 2H), 7.78 (s, 1H), 7.67 (t, 1H), 7.40 (d, 1H), 7.28 (m, 1H), 7.00 (t, 2H), 6.67 (d, 1H), 6.61 (t, 1H), 6.42 (d, 1H), 5.20 (s, 2H), 5.09 (s, 2H), 4.77 (s, 2H).

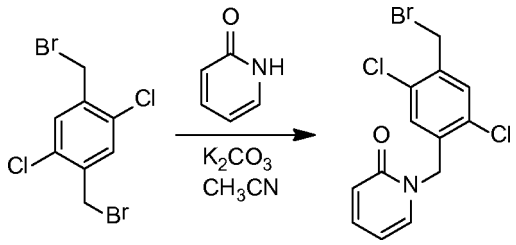
Example 65: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2,5-dichloro-4-((2- oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



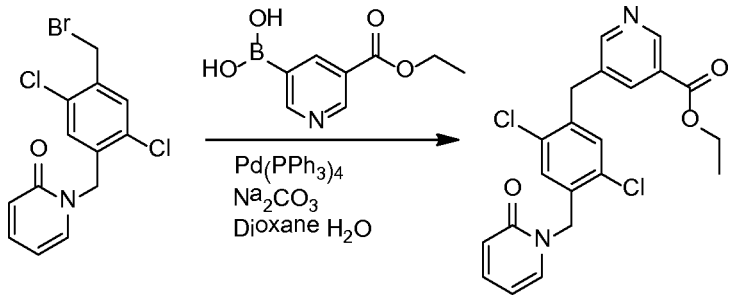
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



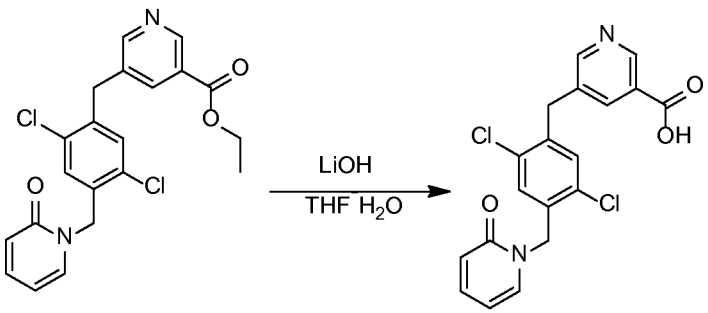
A mixture of 1,4-dichloro-2,5-dimethylbenzene (5 g, 0.03 mol, 1.0 eq), NBS (10.5 g, 0.06 mol) and AIBN (50 mg, 0.3 mmol) in CCl_4 (200 mL) was heated at 85 °C under N_2 for 2 h. The solvents were evaporated, diluted with water (200 mL) and extracted with DCM (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via flash chromatography (PE) to afford 1,4-bis(bromomethyl)-2,5-dichlorobenzene as a white solid (850 mg, 10%).



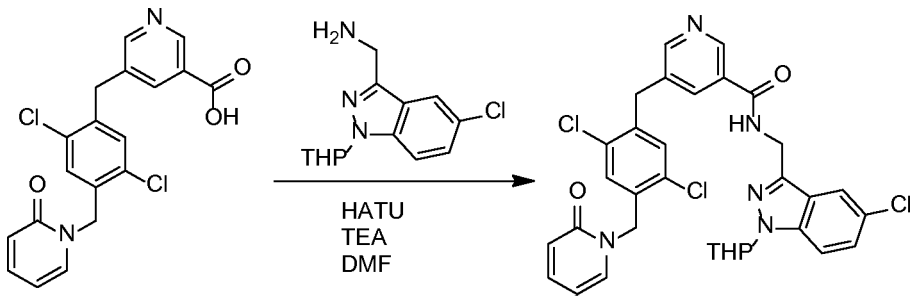
A mixture of 1,4-bis(bromomethyl)-2,5-dichlorobenzene (300 mg, 0.91 mmol), pyridin-2(1H)-one (86 mg, 0.91 mmol) and K_2CO_3 (152 mg, 1.0 mmol) in CH_3CN (5 mL) was heated at 80 °C for 4 h. The mixture was diluted with water (100 mL) and extracted with EA (20 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via flash chromatography to afford 1-(4-(bromomethyl)-2,5-dichlorobenzyl)pyridin-2(1H)-one as a white solid (100 mg, 30%).



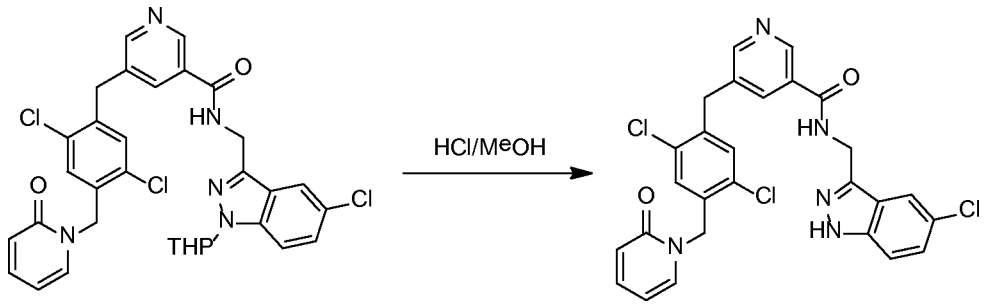
A mixture of 1-(4-(bromomethyl)-2,5-dichlorobenzyl)pyridin-2(1H)-one (100 mg, 0.29 mmol), (5-(ethoxycarbonyl)pyridin-3-yl)boronic acid (65 mg, 0.30 mmol), $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) and Na_2CO_3 (92 mg, 0.87 mmol) in 1,4-dioxane (10 mL) and H_2O (1 mL) was heated at 85 °C for overnight. The mixture was diluted with water (100 mL) and extracted with EA (20 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via flash chromatography to afford ethyl 5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate as a colorness oil (50 mg, 27%).



A solution of ethyl 5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate (50 mg, 0.123 mmol) and LiOH (50 mg, 1.2 mmol) in THF (5 mL) and H_2O (1 mL) was stirred at rt overnight, then concentrated to afford 5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid as a white solid (40 mg, 90%), which was used directly in the next step without further purification.

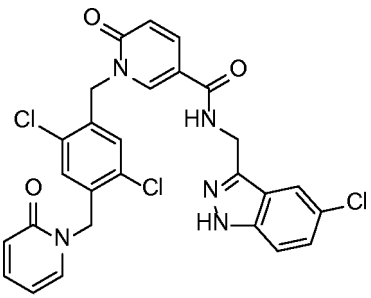


A mixture of 5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (180 mg, 0.47 mmol), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (130 mg, 0.47 mmol), HATU (265 mg, 0.71 mmol) and TEA (0.2 mL, 1.4 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was concentrated and purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (50 mg, 46%).

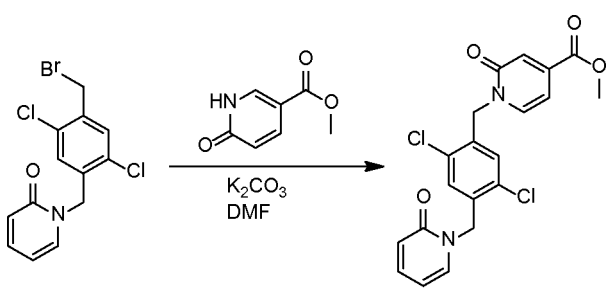


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (50 mg, 0.06 mmol) in HCl/MeOH (5 mL) was stirred at rt for overnight. The mixture was concentrated and purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (30 mg, 80%). LRMS ($M+H^+$) m/z calculated 552, found 552.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.22 (s, 1 H), 8.94 (s, 1 H), 8.89 (s, 1 H), 7.94 (s, 1 H), 7.93-7.91 (d, 1 H), 7.80-7.76 (m, 1 H), 7.68 (s, 1 H), 7.55-7.53 (d, 1 H), 7.42-7.39 (m, 1 H), 7.20 (s, 1 H), 6.79-6.77 (d, 1 H), 6.70-6.66 (m, 1 H), 5.37 (s, 2 H), 4.98 (s, 2 H), 4.43 (s, 2 H).

Example 66: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

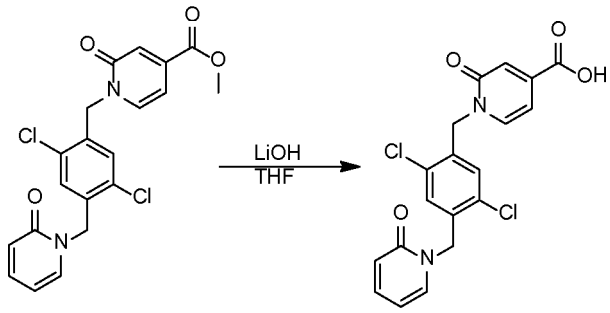


N-((5-chloro-1H-indazol-3-yl)methyl)-1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

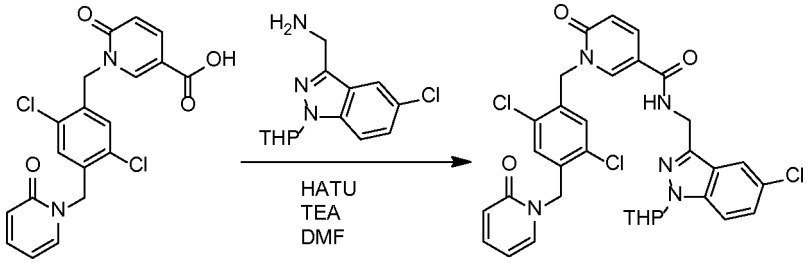


A mixture of 1-(4-(bromomethyl)-2,5-dichlorobenzyl)pyridin-2(1H)-one (150 mg, 0.43 mmol), K_2CO_3 (180 mg, 1.30 mmol) and methyl 6-oxo-1,6-dihydropyridine-3-carboxylate (73 mg, 0.48 mmol) in DMF (5 mL)

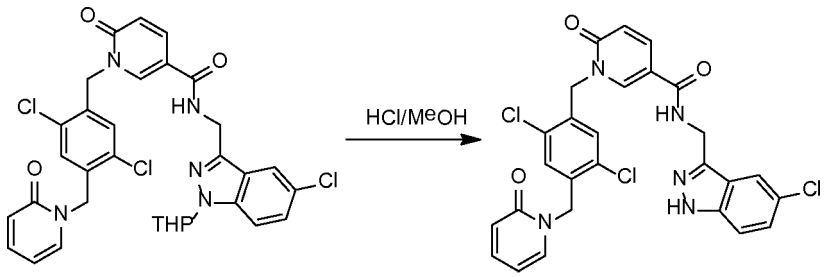
was stirred at rt for overnight. The mixture was diluted with water (100 mL) and extracted with EA (50 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via flash chromatography to afford methyl 1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-2-oxo-1,2-dihydropyridine-4-carboxylate as a colorless oil (170 mg, 90%).



A solution of methyl 1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (180 mg, 0.43 mmol) and LiOH (180 mg, 4.3 mmol) in THF (10 mL) and H_2O (1 mL) was stirred at rt for overnight, then concentrated to afford 1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-2-oxo-1,2-dihydropyridine-4-carboxylic acid as a yellow solid (150 mg, 86%), which was used directly in the next step without further purification.



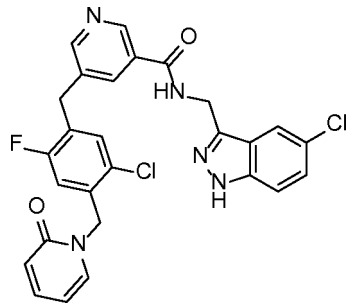
A mixture of 1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-2-oxo-1,2-dihydropyridine-4-carboxylic acid (180 mg, 0.43 mmol), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (130 mg, 0.47 mmol), HATU (250 mg, 0.71 mmol) and TEA (130 mg, 1.40 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide as a white solid (60 mg, 40%).



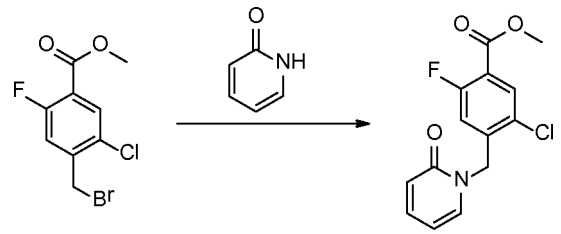
A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (60 mg, 0.09 mmol) in HCl/MeOH (5 mL) was stirred at rt for overnight. The mixture was concentrated and purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-

oxo-1,6-dihydropyridine-3-carboxamide as a white solid (30 mg, 60%). LRMS ($M+H^+$) m/z calculated 568, found 568.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.20 (s, 1 H), 7.85-7.82 (d, 1 H), 7.69(s, 1 H), 7.54-7.52 (d, 1 H), 7.44-7.43 (m, 1 H), 7.33-7.31(d, 1 H), 7.20-7.18 (d, 1 H), 7.01 (s, 1 H), 6.97 (s, 1 H), 6.47-6.44 (m, 2 H), 6.31-6.29 (m, 1 H), 5.11-5.09 (d, 4 H), 4.77 (s, 2 H).

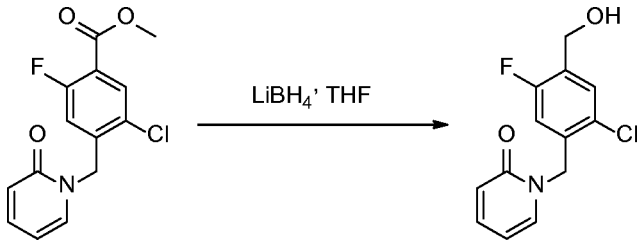
Example 67: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



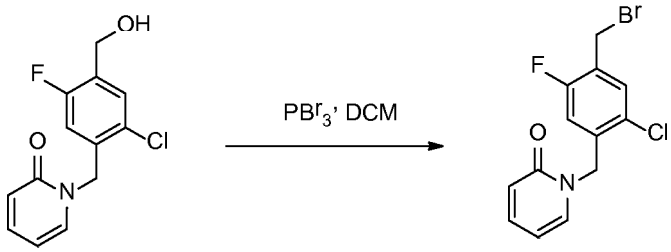
N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



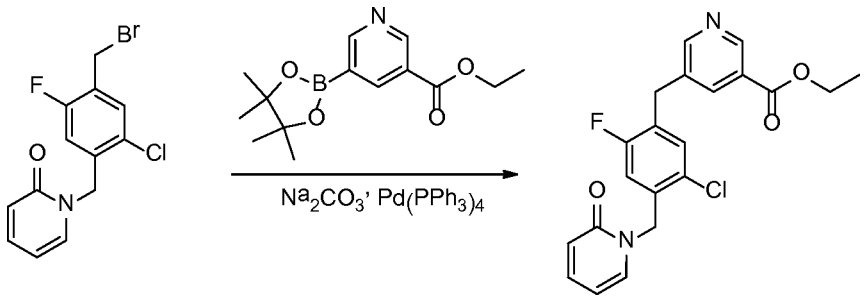
To a solution of methyl 4-(bromomethyl)-5-chloro-2-fluorobenzoate (400 mg, 1.42 mmol, 1.2 eq) in CH_3CN were added pyridin-2(1H)-one (162 mg, 1.70 mmol, 1.2 eq), K_2CO_3 (393 mg, 2.84 mmol), and the mixture was stirred at 60 °C for 3 h. The reaction mixture was concentrated and purified by flash chromatography to afford methyl 5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate as a white solid (380 mg, 96%).



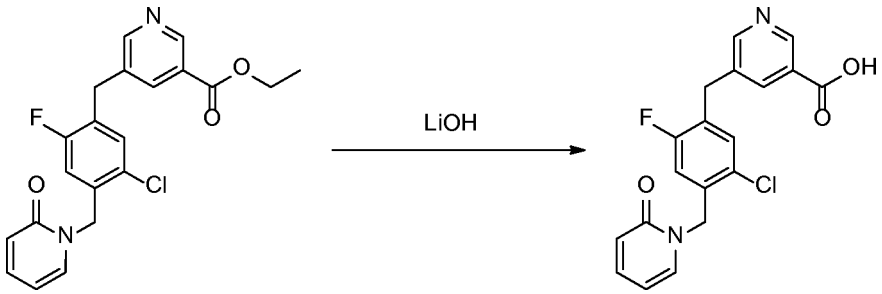
To a solution of methyl 5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate (400 mg, 1.43 mmol, 1 eq) in THF was added $LiBH_4$ (624 mg, 28.6 mmol, 20 eq) under N_2. The mixture was stirred at 70 °C for 5 h. The reaction mixture was concentrated and purified by flash chromatography to afford 1-(2-chloro-5-fluoro-4-(hydroxymethyl)benzyl)pyridin-2(1H)-one as a yellow oil (350 mg, 97 %).



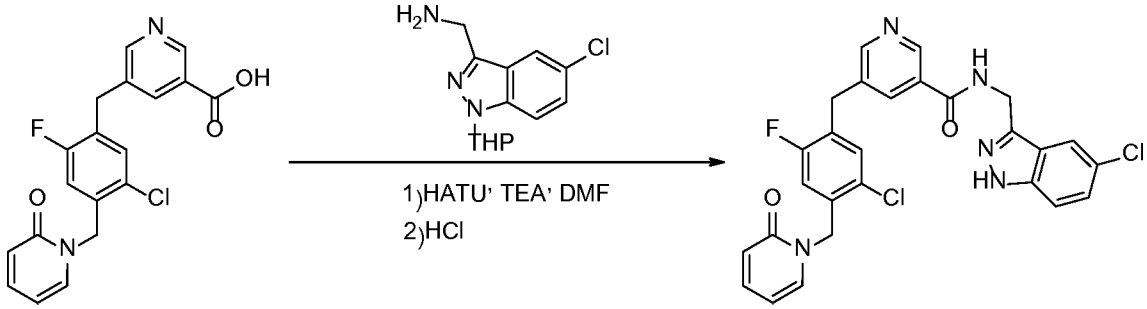
To a solution of 1-(2-chloro-5-fluoro-4-(hydroxymethyl)benzyl)pyridin-2(1H)-one (300 mg, 1.12 mmol, 1 eq) in DCM was added PBr_3, and the mixture was stirred at rt for 3 h. The reaction mixture was poured into ice-water and extracted with DCM; the organic phase was washed with $NaHCO_3$ (aq), concentrated and purified by p-TLC to afford 1-(4-(bromomethyl)-2-chloro-5-fluorobenzyl)pyridin-2(1H)-one as a white solid (170 mg, 45 %).



To a solution of 1-(4-(bromomethyl)-2-chloro-5-fluorobenzyl)pyridin-2(1H)-one (170 mg, 0.513 mmol) in Dioxane /H_2O were added ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (142 mg, 0.513 mmol, 1 eq), Na_2CO_3 (163 mg, 1.539 mmol, 3 eq) and $Pd(PPh_3)_4$ under N_2. The mixture was stirred at 80 °C for 5 h. The reaction mixture was concentrated and purified by prep-TLC to afford ethyl 5-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate as a yellow oil (100 mg, 49 %).



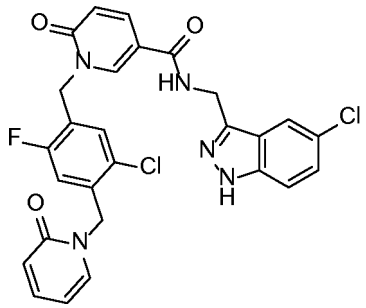
To a solution of ethyl 5-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate (100 mg, 0.25 mmol, 1eq) in THF/H_2O was added LiOH (60 mg, 2.50 mmol, 10 eq). The mixture was stirred rt overnight. It was concentrated and used for next step without further purification.



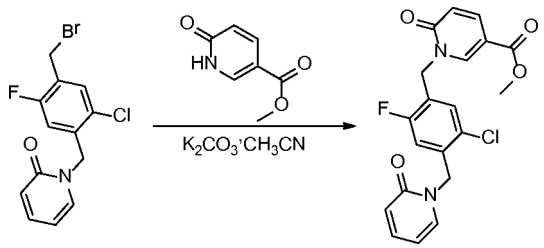
To a solution of 5-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (100 mg, 0.27 mmol, 1 eq) in DMF was added (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (100 mg, 0.38 mmol, 1.4 eq), TEA (82 mg, 0.81 mmol, 3 eq), HATU (144 mg, 0.38 mmol). The mixture was stirred at rt for 5 h. The reaction mixture was concentrated and purified by prep-TLC to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (100 mg). It (100 mg, 0.16 mmol) was dissolved in MeOH (HCl) and stirred for 2h, concentrated and purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(5-chloro-

2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (20 mg, 23 %). LRMS ($M+H^+$) m/z calculated 536.1, found 536.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.84 (s, 1 H), 8.57 (s, 1 H), 8.08 (s, 1 H), 7.85 (s, 1 H), 7.66-7.32 (m , 5 H), 6.78 (d, 1H), 6.58 (d, 1 H), 5.22 (s, 2 H), 4.07 (s, 2 H), 3.33 (s, 2 H).

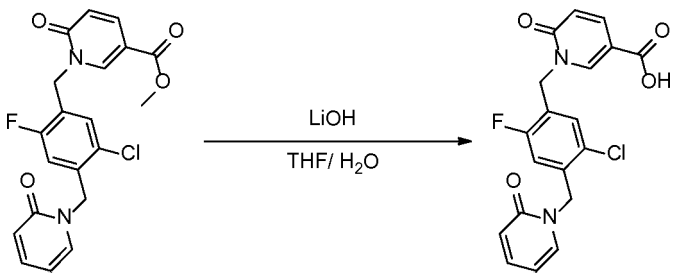
Example 68: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-1-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



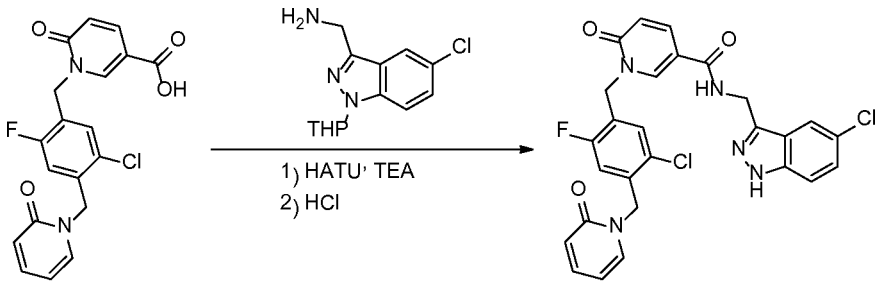
N-((5-chloro-1H-indazol-3-yl)methyl)-1-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



To a solution of 1-(4-(bromomethyl)-2-chloro-5-fluorobenzyl)pyridin-2(1H)-one (300 mg, 0.907 mmol, 1 eq) in DMF was added methyl 6-oxo-1,6-dihydropyridine-3-carboxylate (208 mg, 1.36 mmol, 1.5 eq) and K_2CO_3. The mixture was stirred at rt overnight, then poured into water and extracted with EtOAc. The organic layers were concentrated, purified by prep-TLC (DCM/MeOH = 10/1) to afford methyl 1-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo- 1,6-dihydropyridine-3-carboxylate (100 mg, 27%).

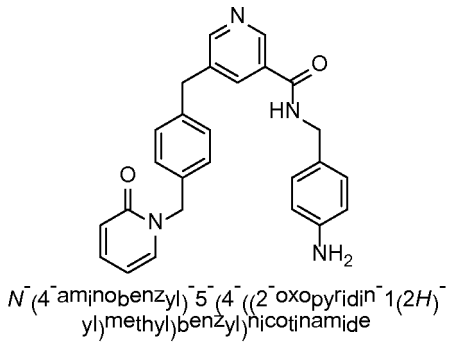


To a solution of methyl 1-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (100 mg, 0.248 mmol, 1 eq) in THF/H_2O was added LiOH (60 mg, 2.48 mmol, 10 eq). The mixture was stirred at rt overnight, then concentrated. The residue was used for the next step without further purification.

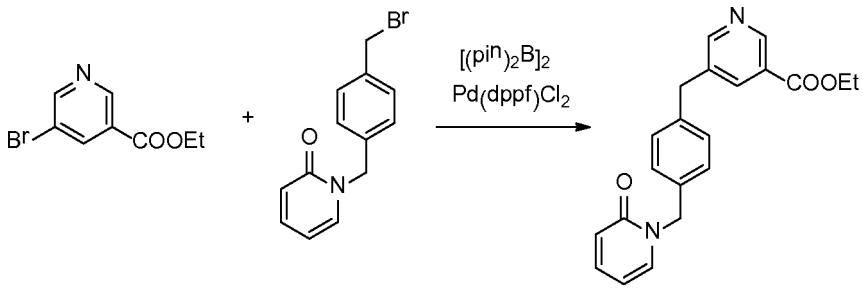


To a solution of 1-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (100 mg, 0.257 mmol, 1 eq) in DMF were added (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (103 mg, 0.257 mmol, 1 eq), TEA (52 mg, 0.514 mmol, 2 eq), HATU (147 mg, 0.386 mmol, 1.5 eq). The mixture was stirred at rt overnight, poured into water and extracted with EtOAc. The organics was concentrated, purified by prep-TLC to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-1-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (100 mg, 61 %). It was dissolved in MeOH (HCl); the mixture was stirred at rt overnight, concentrated and purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-1-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide as a white solid (10 mg, 12%). LRMS ($M+H^+$) m/z calculated 552.1, found 552.1. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 13.17-13.06 (m, 1 H), 8.96-8.92 (m, 1 H), 8.50 (s, 1 H), 7.96-7.89 (m, 2 H), 7.75-7.71 (m , 1 H), 7.54-7.48 (m, 2H), 7.38-7.32 (m, 2 H), 6.68 (d, 1 H), 6.46-6.27 (m, 3 H), 5.17-4.74 (m, 6 H).

Example 69: Preparation of N-(4-aminobenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

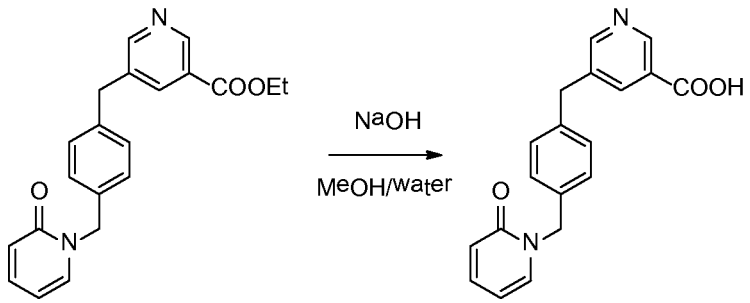


N-(4-aminobenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

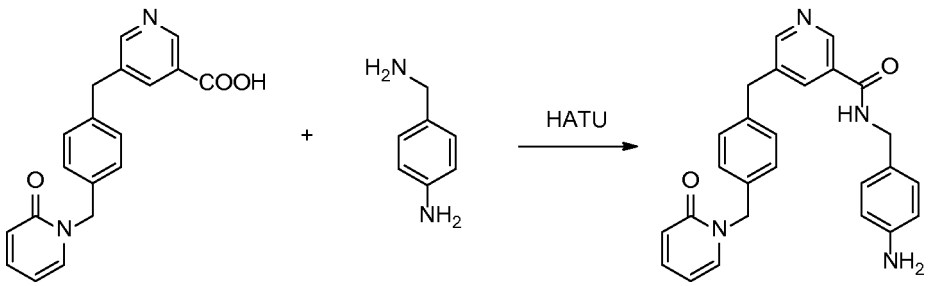


A mixture of methyl ethyl 5-bromonicotinate (5.0 g, 21.73 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.5 g, 21.73 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (790 mg, 1.08 mmol, 5%) and KOAc (6.4 g, 65.21 mmol, 3.0 eq) in dioxane (180 mL) was degassed with N_2 and stirred at 85 °C for 3 h, cooled, 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (6.0 g, 21.73 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (790 mg, 1.08 mmol, 5%) and an aqueous solution of Na_2CO_3 (6.9 g, 65.21 mmol, 3.0 eq) in 30 mL of water were added. The mixture

was degassed and stirred at 95 °C under N_2 overnight. Cooled and filtered through celite, concentrated, the residue was dissolved in DCM (150 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via silica gel column chromatography (5% MeOH in DCM) then purified by flash chromatography to afford ethyl 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate as a yellow solid (4.17 g, 55.1%).

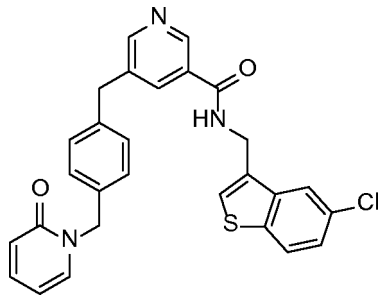


To a stirred solution of methyl ethyl 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinate (2.5 g, 7.18 mmol, 1.0 eq) in MeOH (15 mL) was added an aqueous solution of NaOH (570 mg, 14.36 mmol, 2.0 eq) in water (10 mL). The mixture was stirred at ambient temperature for 1.5 h, concentrated, the residue was acidified with 2 N HCl till pH value was 1, concentrated in vacuo, the residue was dissolved in 10% MeOH in DCM, filtered, the filtrate was concentrated to dryness to afford 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid as an off-white solid (1.9 g, 85%).

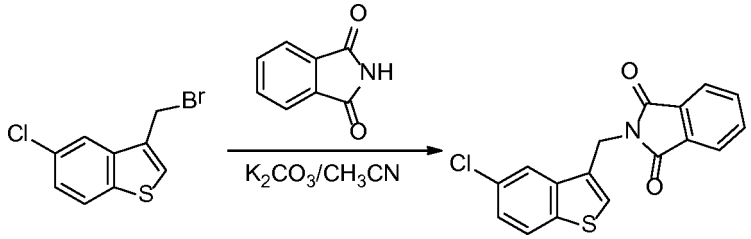


To a stirred mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (100 mg, 0.31 mmol, 1.0 eq) and HATU (178 mg, 0.46 mmol, 1.5 eq) in DMF (4 mL) was added 4-(aminomethyl)aniline (90 mg, 0.73 mmol, 2.3 eq) at 10 °C, the mixture was stirred for 20 min, TEA (0.5 mL) was added. The reaction was stirred at ambient temperature overnight, poured into water, extracted with DCM (15 mL X 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified via prep-HPLC to afford N-(4-aminobenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (30 mg, 22%). LRMS ($M+H^+$) m/z calculated 425.2, found 425.2. ^1H NMR (DMSO-d6, 400 MHz) δ 9.00 (t, 1 H), 8.84 (s, 1 H), 8.60 (s, 1 H), 8.02 (s, 1 H), 7.75 (dd, 1 H), 7.40 (t, 1 H), 7.25-7.20 (m, 4 H) , 6.96 (d, 2 H) , 6.49 (d, 2 H) , 6.39 (d, 1 H) , 6.20 (t, 1 H), 5.04 (s, 2 H), 4.97 (s, 2 H), 4.28 (d, 2 H), 3.98 (s, 2 H).

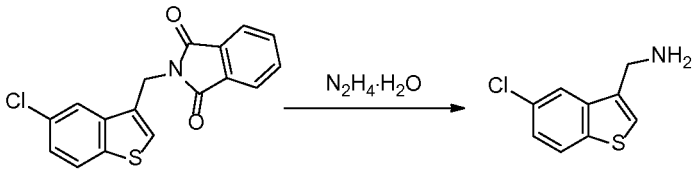
Example 70: Preparation of N-((5-chlorobenzo[b]thiophen-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



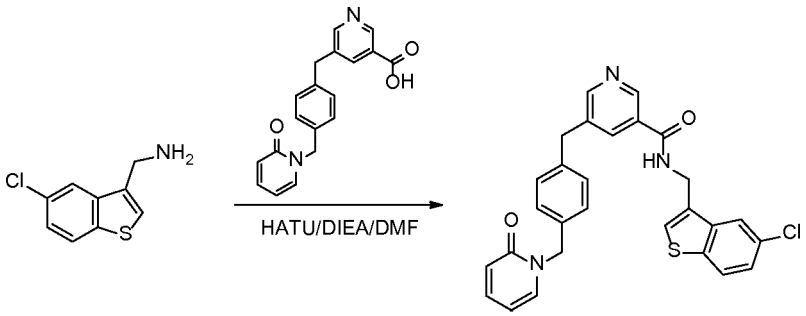
N-((5-chlorobenzo[*b*]thiophen-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



The mixture of 3-(bromomethyl)-5-chlorobenzo[b]thiophene (500 mg, 1.9 mmol, 1.0 eq), isoindoline-1,3-dione (335 mg, 2.28 mmol, 1.2 eq) and K_2CO_3 (498 mg, 3.61 mmol, 3.0 eq) in CH_3CN (20 mL) was stirred at 80 °C overnight. Then the mixture was cooled to rt and filtered. The filtrate was concentrated. The residue was diluted with water (50 mL), extracted with EtOAc (30 mL X 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was dried to afford 2-((5-chlorobenzo[b]thiophen-3-yl)methyl)isoindoline-1,3-dione as a yellow solid (600 mg, 96%).



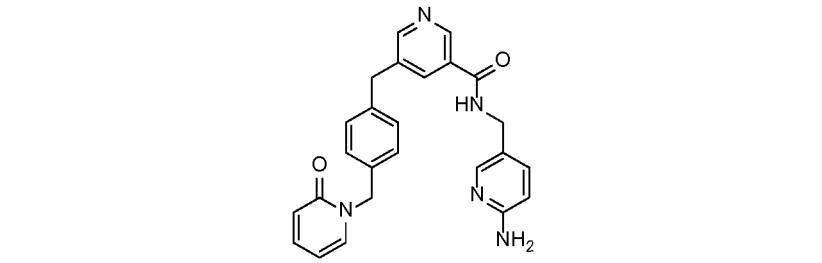
To a suspension of 2-((5-chlorobenzo[b]thiophen-3-yl)methyl)isoindoline-1,3-dione (600 mg, 1.83 mmol, 1.0 eq) in DCM/THF (3 mL/2 mL) was added $N_2H_4.H_2O$ (458 mg, 9.16 mmol, 5.0 eq). The mixture was stirred at rt overnight. Then the mixture was concentrated. The residue was purified on silica gel column (PE/EtOAc = 2/1) to give (5-chlorobenzo[b]thiophen-3-yl)methanamine as a white solid (280 mg, 77%).



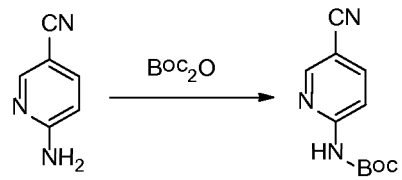
A mixture of (5-chlorobenzo[b]thiophen-3-yl)methanamine (60 mg, 0.3 mmol, 1.0 eq), 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (97 mg, 0.3 mmol, 1.0 eq), HATU (171 mg, 0.45 mmol, 1.5 eq) and DIEA (116 mg, 0.9 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt overnight. The mixture was poured into water (50 mL). The precipitate was collected and purified by pre-HPLC to afford N-((5-chlorobenzo[b]thiophen-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (6.2 mg, 4%). LRMS ($M+H^+$) m/z calculated 500.12, found 500.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.83

(s, 1H), 8.57 (s, 1H), 8.08 (s, 1H), 7.97 (s, 1H), 7.88 (d, 1H), 7.69 (d, 1H), 7.62 (s, 1H), 7.53 (td, 1H), 7.37 (d, 1H), 7.28-7.23 (m, 4H), 6.57 (d, 1H), 6.39 (d, 1H), 5.17 (s, 2H), 4.79 (s, 2H), 4.07 (s, 2H).

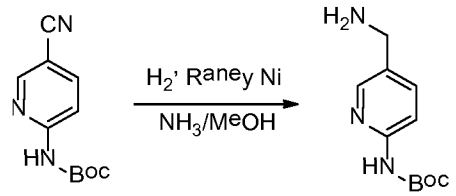
Example 71: Preparation of N-((6-aminopyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



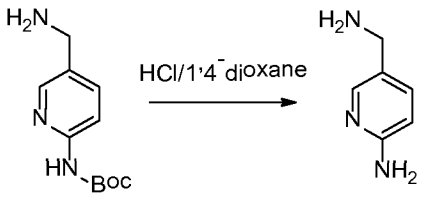
N-((6-aminopyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



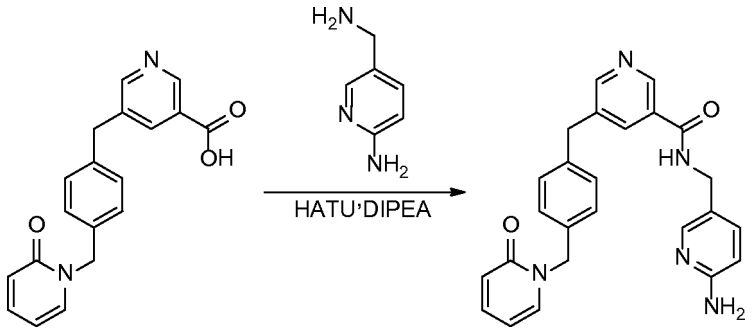
To a solution of 6-aminonicotinonitrile (1.0 g, 8.4 mmol, 1.0 eq) in DCM (10 mL) was added Et_3N (1.7 g, 16.8 mmol, 2.0 eq), DMAP (102 mg, 0.84 mmol, 0.1 eq) and Boc_2O (3.7 g, 16.8 mmol, 2.0 eq) at rt. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford *tert*-butyl (5-cyanopyridin-2-yl)carbamate as a white solid (1.7 g, 92%).



To a solution of *tert*-butyl (5-cyanopyridin-2-yl)carbamate (500 mg, 2.28 mmol, 1.0 eq) in NH_3/MeOH (10 mL) was added Raney Ni (about 100 mg). The mixture was hydrogenated at rt overnight. The mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford *tert*-butyl (5-(aminomethyl)pyridin-2-yl)carbamate as a white solid (240 mg, 47%).

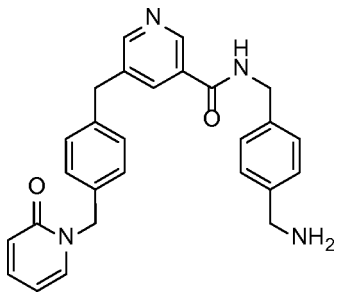


To a solution of *tert*-butyl (5-(aminomethyl)pyridin-2-yl)carbamate (240 mg, 1.08 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/1,4-dioxane (2 mL). The mixture was stirred at rt for 2 h. The mixture was concentrated to dryness under reduced pressure to afford 5-(aminomethyl)pyridin-2-amine as a white solid (300 mg crude, quant).

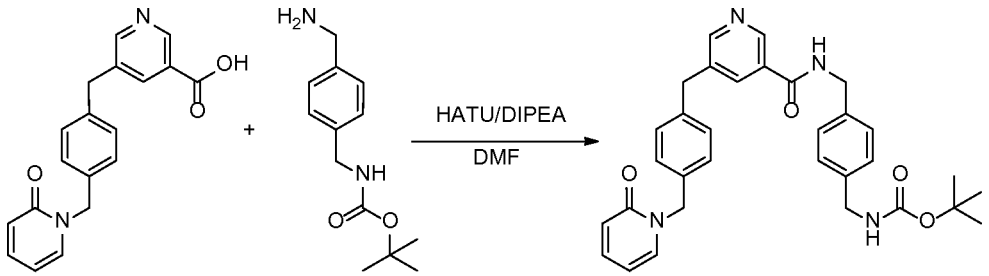


To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (100 mg, 0.31 mmol, 1.0 eq) in DMF (2 mL) was added DIPEA (200 mg, 1.55 mmol, 5.0 eq), HATU (141 mg, 0.37 mmol, 1.2 eq) and 5-(aminomethyl)pyridin-2-amine (300 mg crude, 1.08 mmol, 3.5 eq). The mixture was stirred at rt overnight. The mixture was added water (10 mL), extracted with EA (10 mL x 3), the combined organic layer was washed with brine (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography chromatography to afford N-((6-aminopyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (38 mg, 29%). LRMS ($M+H^+$) m/z calculated 426.2, found 426.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.02 (t, 1 H), 8.83 (s, 1 H), 8.61 (s, 1 H), 8.01 (s, 1 H), 7.85 (s, 1 H), 7.75 (d, 1 H), 7.40 (td, 1 H), 7.33 (d, 1 H), 7.30-7.20 (m, 4 H), 6.45-6.35 (m, 2 H), 6.21 (t, 1 H), 5.87 (brs, 2 H), 5.04 (s, 2 H), 4.25 (d, 2 H), 3.98 (s, 2 H).

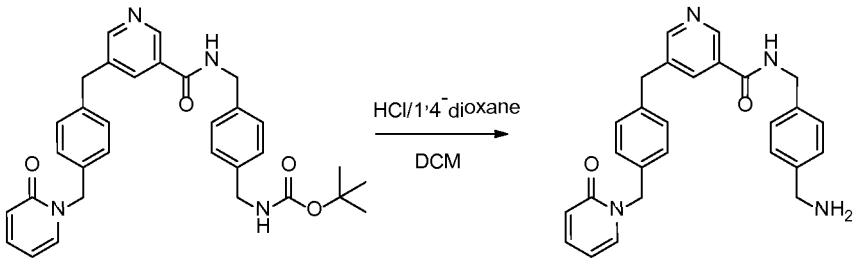
Example 72: Preparation of N-(4-(aminomethyl)benzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



N-(4-(aminomethyl)benzyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

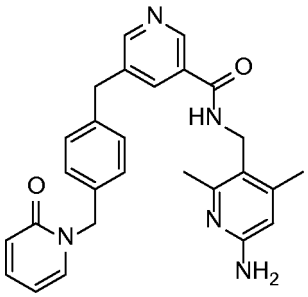


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (160 mg, 0.5 mmol, 1.0 eq.), *tert*-butyl 4-(aminomethyl)benzylcarbamate (142 mg, 0.6 mmol, 1.2 eq.), HATU (250 mg, 1.3 mmol, 1.3 eq.) and DIPEA (0.8 mL) in DMF (5 mL) was stirred at 50 °C overnight. The mixture was poured into water (20 mL) and filtered. The solid was collected to afford *tert*-butyl 4-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)benzylcarbamate as a yellow solid (230 mg, 85.5%).

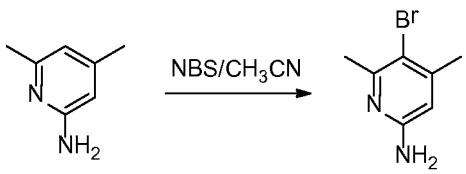


A solution of *tert*-butyl 4-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)benzylcarbamate (101 mg, 0.188 mmol, 1 eq.) in DCM (2 mL) and HCl/dioxane (5 N, 2 mL) was stirred at rt for 2 h, then concentrated. The residue was triturated with DCM/MeOH = 10/1, v/v) to afford N-(4-(aminomethyl)benzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide hydrochloride as a brown solid (80 mg, 89.9%). LRMS ($M+H^+$) m/z calculated 439.2, found 439.2. ^1H NMR (CD_3OD, 400 MHz): δ 9.17 (s, 1 H), 7.84 (d, 1 H), 7.65 (t-d, 1 H),7.50-7.45 (m, 4 H), 7.35 (s, 4 H), 6.67 (d, 1 H), 6.54 (t, 1 H), 5.25 (s, 2 H), 4.65 (s, 2 H), 4.32 (s, 2 H), 4.13 (s, 2 H).

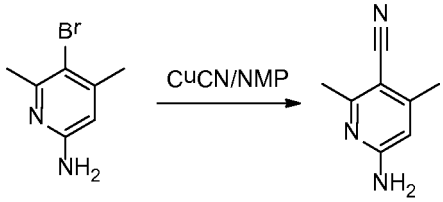
Example 73: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

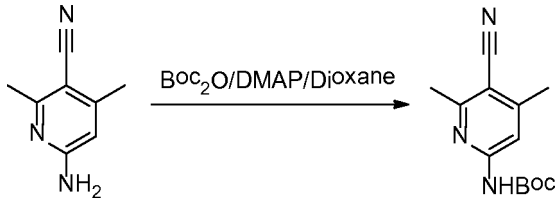


The mixture of 4,6-dimethylpyridin-2-amine (1 g, 8.2 mmol, 1.0 eq) and NBS (1.46 g, 8.2 mmol, 1.0 eq) in CH_3CN (30 mL) was stirred at rt overnight. Then the mixture was concentrated, and the residue was purified on silica gel column (PE/EtOAc = 5/1) to afford 5-bromo-4,6-dimethylpyridin-2-amine as a yellow solid (800 mg, 48%).

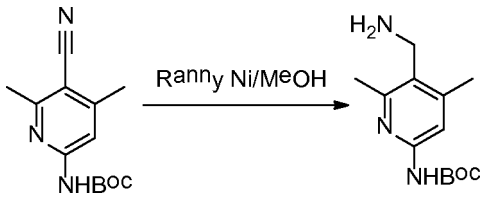


The mixture of 5-bromo-4,6-dimethylpyridin-2-amine (800 mg, 3.98 mmol, 1.0 eq) and CuCN (425 mg, 4.78 mmol, 1.2 eq) in NMP (10 mL) was stirred at 200 °C for 1 h with microwave. Then the mixture was cooled to

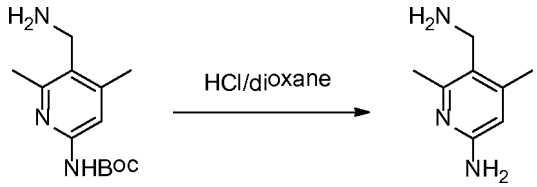
rt and directly purified by flash chromatography to give 6-amino-2,4-dimethylnicotinonitrile as a brown oil (585 mg, crude, include NMP).



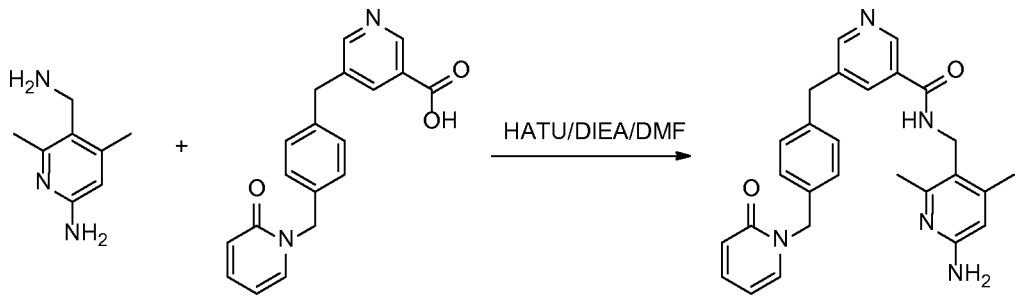
A mixture of 6-amino-2,4-dimethylnicotinonitrile (585 mg, 3.98 mmol, 1.0 eq), Boc_2O (1.74 g, 7.96 mmol, 2.0 eq), TEA (1.2 g, 12mmol, 3.0 eq) and DMAP (49 mg, 0.4 mmol, 0.1 eq) in 1,4-dioxane (10 mL) was stirred at rt overnight. Then the mixture was purified on silica gel column (PE/EtOAc = 5/1) to afford *tert*-butyl (5-cyano-4,6-dimethylpyridin-2-yl)carbamate as a white solid (720 mg, 73%).



The solutuion of *tert*-butyl (5-cyano-4,6-dimethylpyridin-2-yl)carbamate (720 mg, 2.9 mmol, 1.0 eq) and Raney Ni (20 mg) in MeOH (15 mL) was stirred at rt under H_2 (1 atm) overnight. Then the mixture was filtered and the filtrate was concentrated to give *tert*-butyl (5-(aminomethyl)-4,6-dimethylpyridin-2-yl)carbamate as a colorless oil (720 mg, 99%).



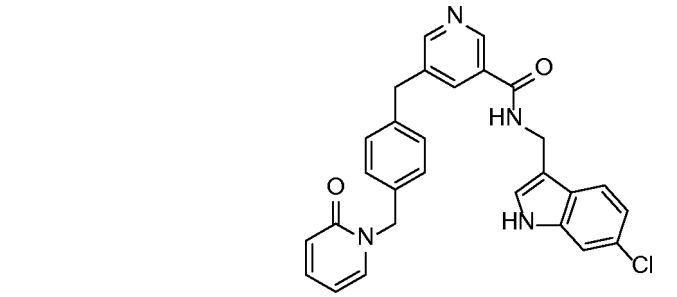
The mixture of *tert*-butyl (5-(aminomethyl)-4,6-dimethylpyridin-2-yl)carbamate (720 mg, 2.9 mmol, 1.0 eq) in 2 N HCl/dioxane (15 mL) and MeOH (3 mL) was stirred at rt overnight. Then the mixture was filtered to give 5-(aminomethyl)-4,6-dimethylpyridin-2-amine as a white solid (349 mg, 79%).



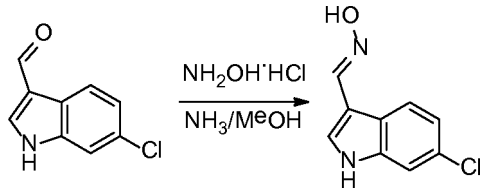
A mixture of 5-(aminomethyl)-4,6-dimethylpyridin-2-amine (117 mg, 0.63 mmol, 1.0 eq), 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (200 mg, 0.63 mmol, 1.0 eq), HATU (479 mg, 1.26 mmol, 2.0 eq) and DIEA (406 mg, 3.15 mmol, 5.0 eq) in DMF (5 mL) was stirred at rt for 2 h. The mixture was poured into water (50 mL), extracted with DCM (30 mLx3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to afford N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-

yl)methyl)benzyl)nicotinamide as a white solid (91.2 mg, 32%). LRMS ($M+H^+$) m/z calculated 454.2, found 454.2. ^1H NMR (DMSO-d6, 400 MHz) δ 8.80 (d, 1H), 8.58 (d, 1H), 7.99 (s, 1H), 7.75 (dd, 1H), 7.40 (td, 1H), 7.22 (s, 4H), 6.39 (d, 1H), 6.23-6.21 (m, 2H), 5.99 (brs, 2H), 5.04 (s, 2H), 4.32 (d, 2H), 3.98 (s, 2H), 2.33 (s, 3H), 2.20 (s, 3H).

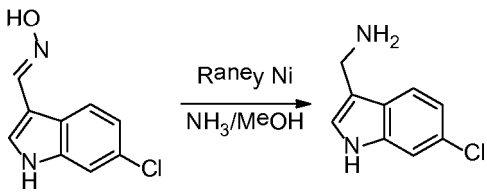
Example 74: Preparation of N-((6-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



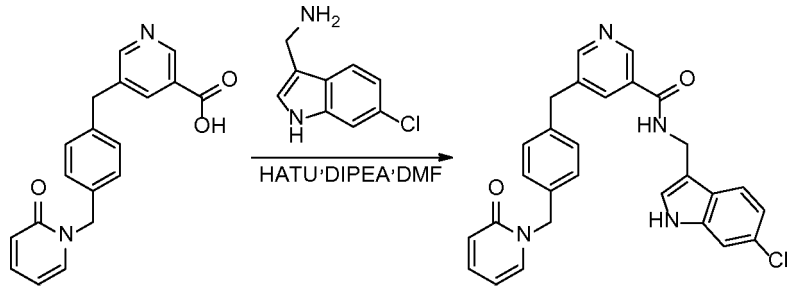
N-((6-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



To a solution of 6-chloro-1H-indole-3-carbaldehyde (1.0 g, 5.66 mmol, 1.0 eq) in NH_3/MeOH (10 mL) was added $NH_2OH.HCl$ (502 mg, 7.2 mmol, 1.3 eq) at rt. The mixture was stirred at rt for 2 h. The mixture was concentrated to dryness under reduced pressure to afford 6-chloro-1H-indole-3-carbaldehyde oxime as a yellow solid (1.6 g crude, quant).



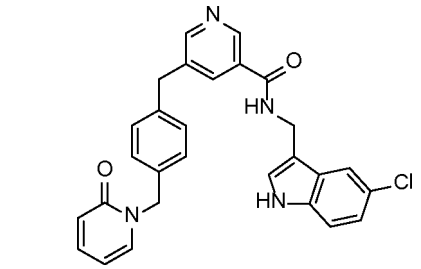
To a solution of 6-chloro-1H-indole-3-carbaldehyde oxime (360 mg, 1.84 mmol, 1.0 eq) in NH_3/MeOH (5 mL) was added Raney Ni (about 36 mg). The suspension was hydrogenated at rt overnight. The mixture was filtered. The filtered cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure to afford (6-chloro-1H-indol-3-yl)methanamine as an off-white solid (330 mg crude, quant).



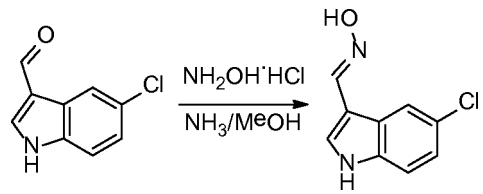
To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (150 mg, 0.47 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (182 mg, 1.41 mmol, 3.0 eq) and HATU (213 mg, 0.56 mmol, 1.2 eq) at 0 °C

under N_2. The mixture was stirred at 0 °C for 30 min, (6-chloro-1H-indol-3-yl)methanamine (93 mg, 0.52 mmol, 1.1 eq) was then added and the mixture was stirred at rt for 2 h under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford 110 mg of product, which was further purified via Prep-HPLC to afford N-((6-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow solid (50 mg, 22%). LRMS ($M+H^+$) m/z caculated 483.1, found 483.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.08 (brs, 1 H), 9.00 (t, 1 H), 8.83 (s, 1 H), 8.59 (s, 1 H), 8.02 (s, 1 H), 7.75 (d, 1 H), 7.62 (d, 1 H), 7.45-7.35 (m, 2 H), 7.34 (s, 1 H), 7.25-7.15 (m, 4 H), 7.00 (d, 1 H), 6.39 (d, 1 H), 6.21 (t, 1 H), 5.04 (s, 2 H), 4.59 (d, 2 H), 3.98 (s, 2 H).

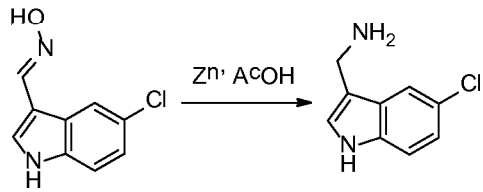
Example 75: Preparation of N-((5-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



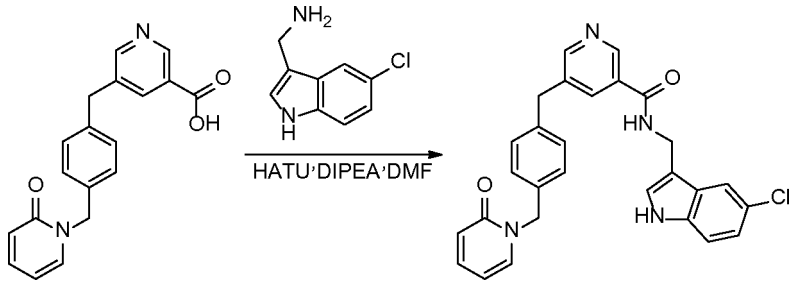
N-((5-chloro-1*H*-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



To a solution of 5-chloro-1H-indole-3-carbaldehyde (1.0 g, 5.66 mmol, 1.0 eq) in NH_3/MeOH (10 mL) was added $NH_2OH.HCl$ (502 mg, 7.2 mmol, 1.3 eq) at rt. The mixture was stirred at rt for 2 h. The mixture was concentrated to dryness under reduced pressure. The crude product was purified via flash chromatography to afford 5-chloro-1H-indole-3-carbaldehyde oxime as a brown solid (0.68 g, 62%).

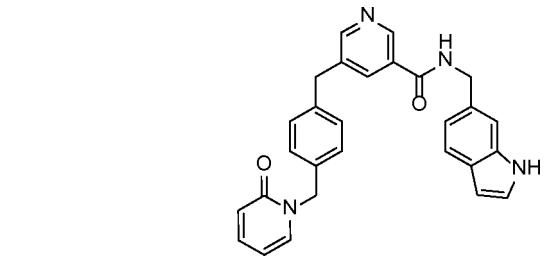


To a solution of 5-chloro-1H-indole-3-carbaldehyde oxime (600 mg, 3.08 mmol, 1.0 eq) in AcOH (10 mL) was added Zn (1.0 g, 15.4 mmol). The suspension was heated to 30 °C overnight. The mixture was concentrated to dryness under reduced pressure. The residue was added water (10 mL), saturated $NaHCO_3$ (20 mL), extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to afford (5-chloro-1H-indol-3-yl)methanamine as a yellow solid (380 mg crude, 68%).

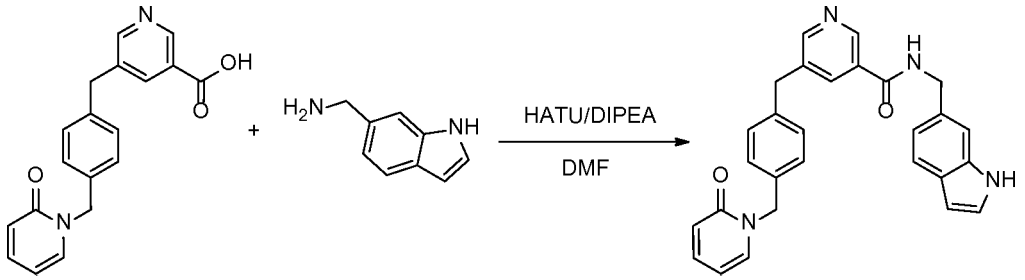


To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (150 mg, 0.47 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (182 mg, 1.41 mmol, 3.0 eq) and HATU (213 mg, 0.56 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1H-indol-3-yl)methanamine (93 mg, 0.52 mmol, 1.1 eq) was then added and the mixture was stirred at rt for 2 h under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (40 mg, 18%). LRMS ($M+H^+$) m/z caculated 483.1, found 483.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.14 (brs, 1 H), 9.02 (t, 1 H), 8.83 (d, 1 H), 8.59 (d, 1 H), 8.01 (s, 1 H), 7.74 (d, 1 H), 7.68 (s, 1 H), 7.45-7.35 (m, 3 H), 7.30-7.15 (m, 4 H), 7.07 (dd, 1 H), 6.39 (d, 1 H), 6.20 (t, 1 H), 5.03 (s, 2 H), 4.56 (d, 2 H), 3.98 (s, 2 H).

Example 76: Preparation of N-((1H-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



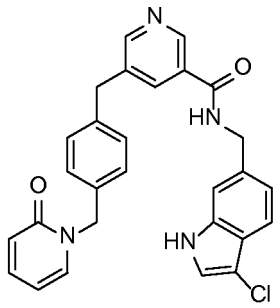
N-((1*H*-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



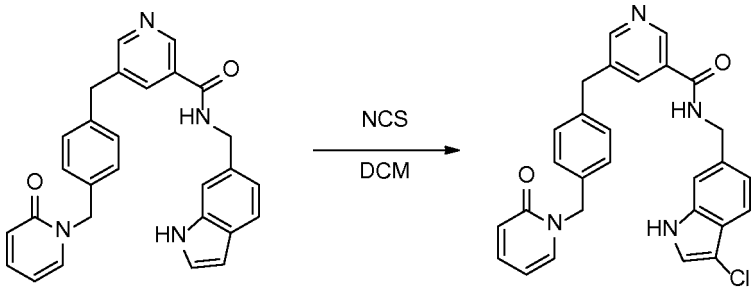
A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (91 mg, 0.28 mmol, 1.0 eq.), (1H-indol-6-yl)methanamine (44 mg, 0.30 mmol, 1.07 eq.), HATU (114 mg, 0.3 mmol, 1.07 eq.) and DIPEA (0.5 mL) in DCM (3 mL) was stirred at rt overnight. Filtered and the solid was collected and triturated with water to afford N-((1H-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (100 mg, 78.7%). LRMS ($M+H^+$) m/z calculated 449.2, found 449.2. ^1H NMR (CD_3OD, 400 MHz) δ

8.85 (s, 1 H), 8.57 (s, 1 H), 8.09 (s, 1 H), 7.69 (d, 1 H), 7.55-7.51 (m, 2 H), 7.39 (t, 1 H), 7.29-7.22 (m, 5 H), 7.03 (d, 1 H), 6.57 (d, 1 H), 6.43-6.37 (m, 2 H), 5.18 (s, 2 H), 4.67 (s, 2 H), 4.08 (s, 2 H).

Example 77: Preparation of N-((3-chloro-1H-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

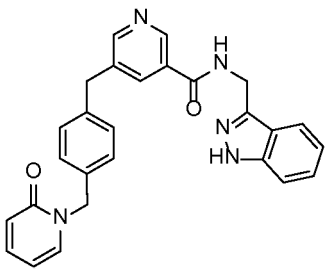


N-((3-chloro-1*H*-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

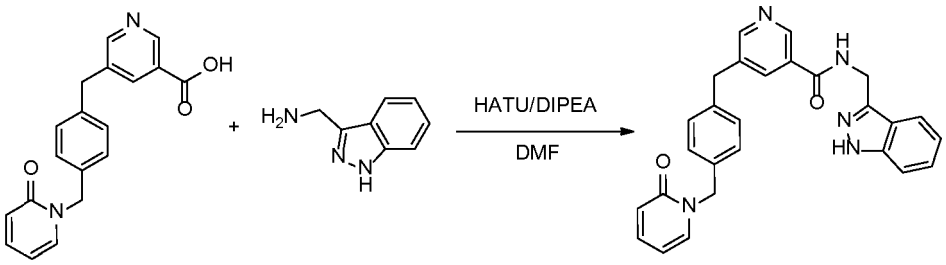


The mixture of N-((1H-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (56 mg, 0.125 mmol, 1.0 eq) in DCM (5 mL) was treated with NCS (16 mg, 0.125 mmol, 1.0 eq). And the reaction was stirred at ambient temperature overnight, concentrated, purified via flash chromatography to afford N-((3-chloro-1H-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (15 mg, 25%). LRMS (M+H$^+$) m/z calculated 483.1, found 483.1. ^{1}HNMR (CD_3OD, 400 MHz) δ 8.73 (s, 1 H), 8.45 (s, 1 H), 7.96 (s, 1 H), 7.56 (d, 1 H), 7.44-7.34 (m, 2 H), 7.26 (s, 1 H), 7.18-7.10 (m, 5 H), 7.01 (d, 1 H), 6.45 (d, 1 H), 6.26 (t, 1 H), 5.05 (s, 2 H), 4.55 (s, 2 H), 3.95 (s, 2 H).

Example 78: Preparation of N-((1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

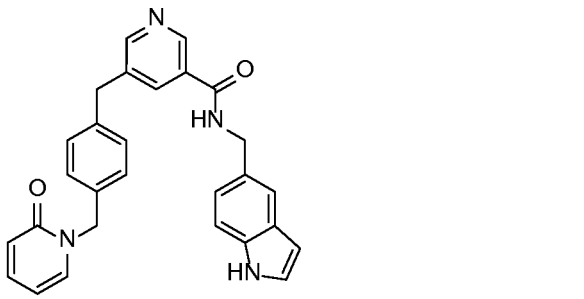


N-((1*H*-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

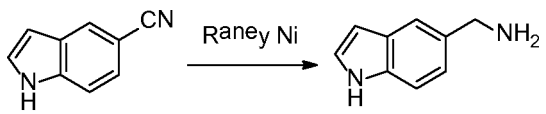


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (91 mg, 0.28 mmol, 1.0 eq), (1H-indazol-3-yl)methanamine (44 mg, 0.30 mmol, 1.07 eq), HATU (114 mg, 0.3 mmol, 1.07 eq) and DIPEA (0.5 mL) in DCM (3 mL) was stirred at rt overnight. Filtered and the solid was collected and purified via prep-MPLC to afford N-((1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (40 mg, 31%). LRMS ($M+H^+$) m/z calculated 450.2, found 450.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.85 (s, 1 H), 8.56 (s, 1 H), 7.83 (d, 1 H), 7.69 (d, 1 H), 7.55-7.50 (m, 2 H), 7.40 (t, 1 H), 7.26 (dd, 4 H), 7.14 (t, 1 H), 6.58 (d, 1 H) , 6.40 (t, 1 H), 5.18 (s, 2 H), 4.96 (s, 2 H), 4.08 (s, 2 H).

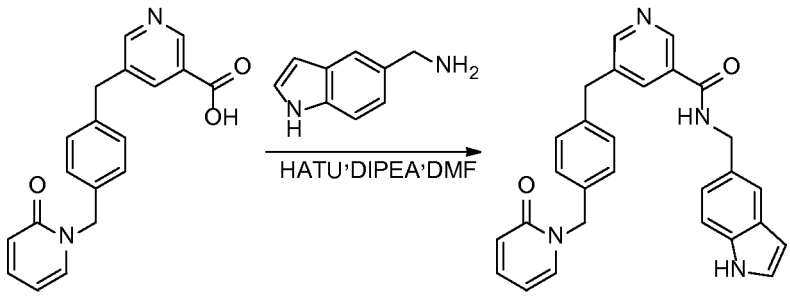
Example 79: Preparation of N-((1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



N-((1*H*-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



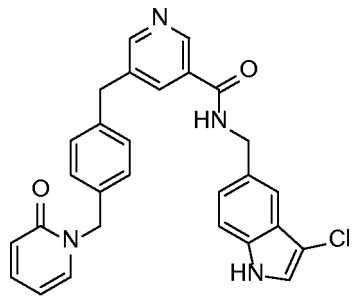
To a solution of 1H-indole-5-carbonitrile (1.0 g, 7.0 mmol, 1.0 eq) in NH_3/MeOH (10 mL) was added Raney Ni (about 100 mg). The suspension was hydrogenated at rt overnight. The mixture was filtered. The filtered cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography to afford (1H-indol-5-yl)methanamine as an off-white solid (330 mg, 32%).



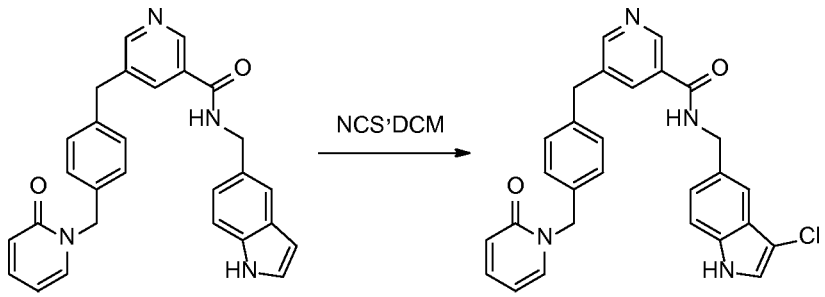
To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (60 mg, 0.19 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (74 mg, 0.57 mmol, 3.0 eq) and HATU (87 mg, 0.23 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (1H-indol-5-yl)methanamine (28 mg, 0.19 mmol, 1.0 eq)

was then added and the mixture was stirred at rt for 2 h under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow solid (30 mg, 35%). LRMS ($M+H^+$) m/z caculated 449.2, found 449.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.03 (brs, 1 H), 9.14 (t, 1 H), 8.88 (d, 1 H), 8.61 (d, 1 H), 8.05 (s, 1 H), 7.75 (dd, 1 H), 7.46 (s, 1 H), 7.45-7.35 (m, 1 H), 7.34-7.30 (m, 2 H), 7.26-7.20 (m, 4 H), 7.05 (d, 1 H), 7.45-7.35 (m, 2 H), 6.20 (t, 1 H), 5.03 (s, 2 H), 4.52 (d, 2 H), 3.99 (s, 2 H).

Example 80: Preparation of N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

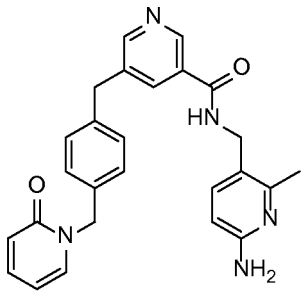


N-((3-chloro-1*H*-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

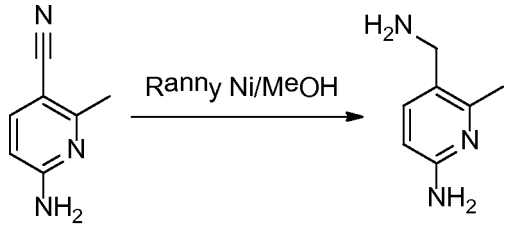


To a solution of N-((1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (100 mg, 0.22 mmol, 1.0 eq) in DCM (5 mL) was added NCS (30 mg, 0.22 mmol, 1.0 eq). The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (30 mg, 28%). LRMS ($M-H^+$) m/z caculated 481.1, found 481.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.33 (brs, 1 H), 9.19 (t, 1 H), 8.87 (s, 1 H), 8.62 (d, 1 H), 8.04 (s, 1 H), 7.75 (d, 1 H), 7.50 (d, 1 H), 7.45-7.30 (m, 3 H), 7.28-7.20 (m, 4 H), 7.16 (d, 1 H), 6.39 (d, 1 H), 6.20 (t, 1 H), 5.03 (s, 2 H), 4.56 (d, 2 H), 3.99 (s, 2 H).

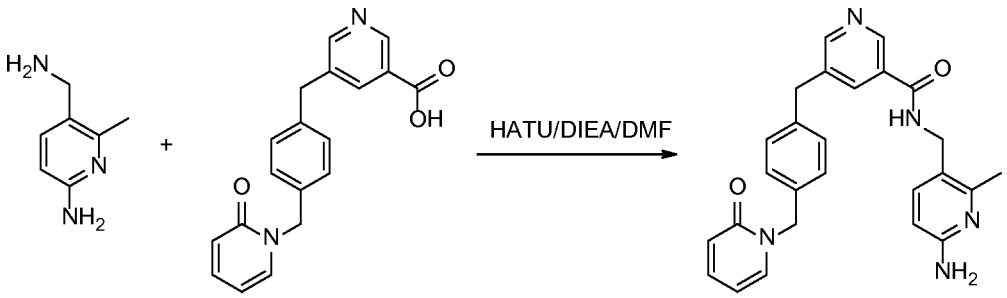
Example 81: Preparation of N-((6-amino-2-methylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



N-((6-amino-2-methylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

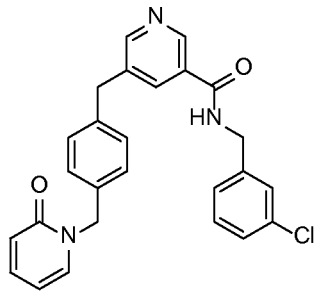


The solutuion of 6-amino-2-methylnicotinonitrile (200 mg, 1.5 mmol, 1.0 eq) and Raney Ni (50 mg) in MeOH (10 mL) was stirred at rt under H_2 (1 atm) overnight. Then the mixture was filtered and the filtrate was concentrated to give 5-(aminomethyl)-6-methylpyridin-2-amine as a yellow solid (210 mg, quant). The solid was used for the next step without further purification.

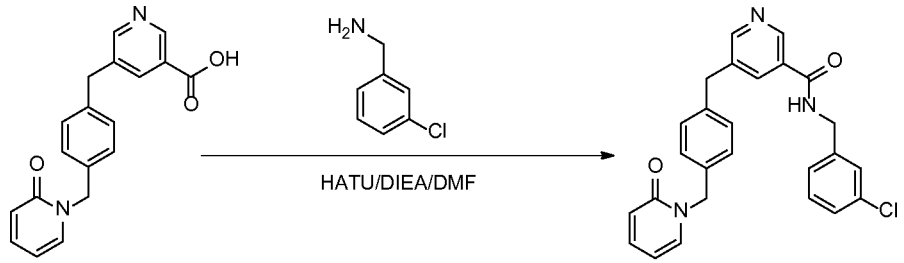


A mixture of 5-(aminomethyl)-6-methylpyridin-2-amine (47 mg, 0.34 mmol, 1.1 eq), 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (100 mg, 0.31 mmol, 1.0 eq), HATU (235 mg, 0.62 mmol, 2.0 eq) and DIEA (120 mg, 0.93 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt for 2 h. The mixture was poured into water (50 mL), extracted with EtOAc (30 mLx3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to afford N-((6-amino-2-methylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (34 mg, 25%). LRMS ($M+H^+$) m/z calculated 440.2, found 440.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.95 (t, 1H), 8.84 (s, 1H), 8.61 (s, 1H), 8.00 (s, 1H), 7.75 (dd, 1H), 7.42-7.38 (m, 2H), 7.24-7.20 (m, 4H), 6.40-6.37 (m, 2H), 6.23-6.19 (m, 2H), 5.04 (s, 2H), 4.28 (d, 2H), 3.99 (s, 2H), 2.33 (s, 3H).

Example 82: Preparation of N-(3-chlorobenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

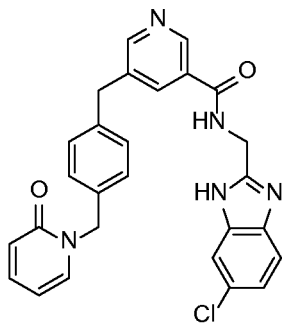


N-(3-chlorobenzyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

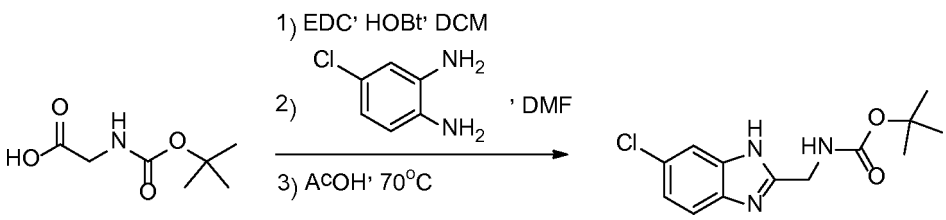


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (100 mg, 0.3 mmol, 1.0 eq), (3-chlorophenyl)methanamine (44 mg, 0.31 mmol, 1.0 eq), HATU (236 mg, 0.6 mmol, 2.0 eq) and DIEA (120 mg, 0.9 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt for 2 h. The mixture was poured into water (50 mL), extracted with EtOAc (30 mLx3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to afford N-(3-chlorobenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow solid (74 mg, 54%). LRMS ($M+H^+$) m/z calculated 444.2, found 444.1. ^1H NMR (DMSO-d6, 400 MHz) δ 9.23 (t, 1H), 8.88 (d, 1H), 8.63 (d, 1H), 8.05 (s, 1H), 7.75 (dd, 1H), 7.42-7.21 (m, 9H), 6.38 (d, 2H), 6.21 (t, 1H), 5.04 (s, 2H), 4.47 (d, 2H), 4.01 (s, 2H).

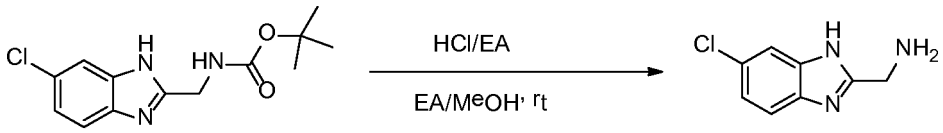
Example 83: Preparation of N-((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)-5-(4-((2-oxopyridin- 1(2H)-yl)methyl)benzyl)nicotinamide



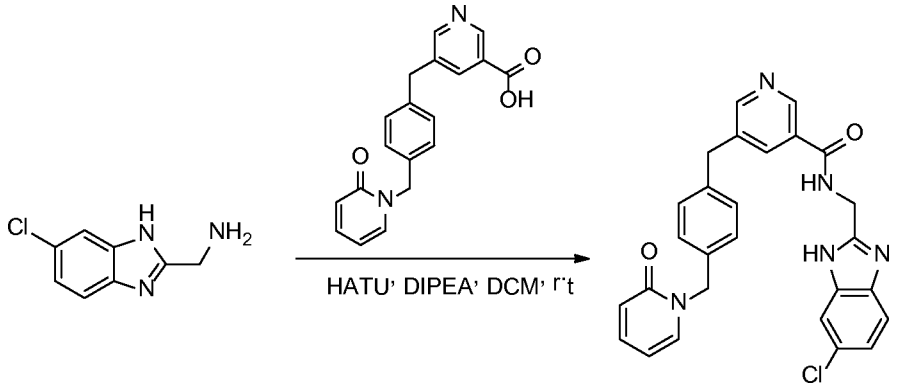
N-((6-chloro-1*H*-benzo[*d*]imidazol-2-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



A mixture of 2-((*tert*-butoxycarbonyl)amino)acetic acid (2.62 g, 15.0 mmol, 1.0 eq), EDC.HCl (3.44 g, 18.0 mmol, 1.2 eq), HOBt (2.83 g, 21.0 mmol, 1.4 eq) and DCM (150 mL) was stirred at rt for 10 min. Then 4-chlorobenzene-1,2-diamine (2.13 g, 15.0 mmol, 1.0 eq) and DMF(2 mL) were added, and the resulting mixture was stirred at rt overnight. DCM was evaporated and EA (150 mL) was added. The organic phase was washed with brine (30 mL), sat. NH_4Cl (30 mL x 2), sat. $NaHCO_3$ (30 mL x 2) and finally with brine (30 mL). The resulting organic layer was dried with Na_2SO_4, concentrated to dryness. Then 20 mL of AcOH was added and the mixture was heated to 70 °C and stirred for 2 h. After cooled to rt, the mixture was concentrated in vacuo to give a solid, purified by flash chromatography to afford *tert*-butyl ((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)carbamate as a yellow solid (3.33 g, 79.1%).

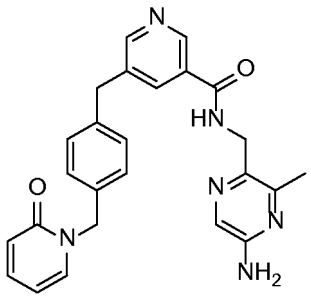


To a solution of *tert*-butyl ((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)carbamate (3.33 g, 11.8 mmol, 1.0 eq) in EA/MeOH (15 mL/60 mL) was added HCl/EA (20 mL). The mixture was stirred at rt overnight. The mixture was concentrated in vacuo to give a pink solid, purified by flash chromatography to afford (6-chloro-1H-benzo[d]imidazol-2-yl)methanamine as a pink oil (1.50 g, 69.8%).

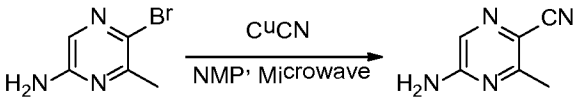


To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (96 mg, 0.30 mmol, 1.0 eq) in DCM (7.5 mL) were added HATU (171 mg, 0.45 mmol, 1.5 eq) and DIPEA (1.5 mL). The mixture was stirred at rt for 5 min. Then (6-chloro-1H-benzo[d]imidazol-2-yl)methanamine (66 mg, 0.36 mmol, 1.2 eq) was added, and the resulting mixture was stirred at rt overnight. The mixture was washed with H_2O (5 mL x 2), sat.NaCl (5 mL), dried with Na_2SO_4, concentrated to dryness to give a yellow solid. The residue was purified by flash chromatography to afford N-((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (120 mg, 82.8%). LRMS ($M+H^+$) m/z calculated 483.1, found 483.1. ^1H NMR (DMSO-*d6*, 400 MHz) δ 8.93 (d, 1H), 8.62 (d, 1H), 8.17 (s, 1H), 7.69 (dd, 1H), 7.53 (m, 3H), 7.27 (m, 5H), 6.57 (d, 1H), 6.39 (t, 1H), 5.18 (s, 2H), 4.82 (s, 2H), 4.10 (s, 2H).

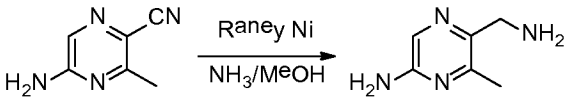
Example 84: Preparation of N-((5-amino-3-methylpyrazin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



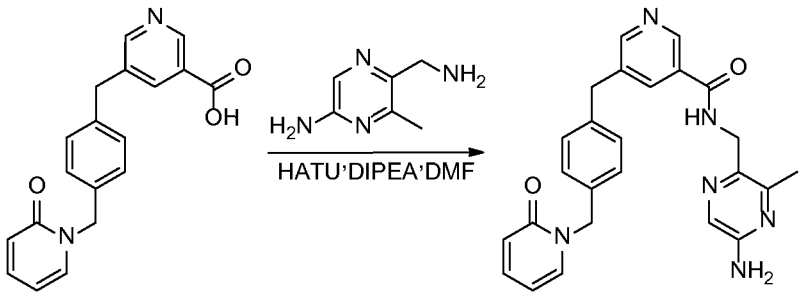
N-((5-amino-3-methylpyrazin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



To a solution of 5-bromo-6-methylpyrazin-2-amine (300 mg, 1.6 mmol, 1.0 eq) in NMP (12 mL) was added CuCN (287 mg, 3.2 mmol, 2.0 eq). The suspension was heated at 200 °C for 1 h in microwave. The reaction mixture was cooled to 25 °C, mixed with water (20 mL), $NH_3.H_2O$ (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford 5-amino-3-methylpyrazine-2-carbonitrile as a brown solid (210 mg, 98%).



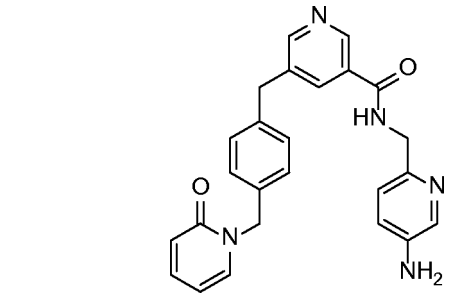
To a solution of 5-amino-3-methylpyrazine-2-carbonitrile (100 mg, 0.75 mmol, 1.0 eq) in NH_3/MeOH (5 mL) was added Raney Ni (about 21 mg). The suspension was hydrogenated at rt overnight. The mixture was filtered. The filtered cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure to afford 5-(aminomethyl)-6-methylpyrazin-2-amine as a yellow solid (130 mg crude, quant).



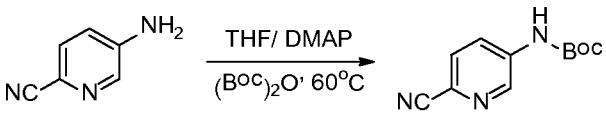
To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (100 mg, 0.31 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (120 mg, 0.93 mmol, 3.0 eq) and HATU (141 mg, 0.37 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, 5-(aminomethyl)-6-methylpyrazin-2-amine (130 mg crude, 0.31 mmol, 1.0 eq) was then added and the mixture was stirred at rt for 2 h under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-amino-3-methylpyrazin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (40 mg, 29%). LRMS ($M+H^+$) m/z caculated 441.2, found 441.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.91 (t, 1 H), 8.84 (s, 1 H), 8.60 (s, 1 H), 8.02 (s, 1 H), 7.75 (dd, 1

H), 7.63 (s, 1 H), 7.50-7.30 (m, 1 H), 7.28-7.20 (m, 4 H), 6.39 (d, 1 H), 6.25-6.18 (m, 3 H), 5.04 (s, 2 H), 4.42 (d, 2 H), 3.98 (s, 2 H), 2.31 (s, 3 H).

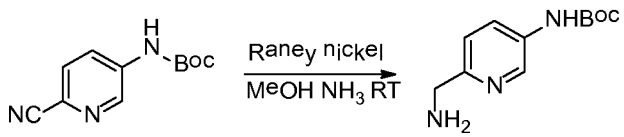
Example 85: Preparation of N-((5-aminopyridin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



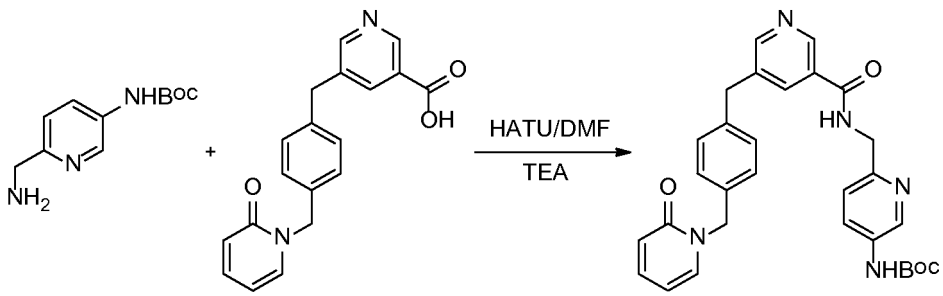
N-((5-aminopyridin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



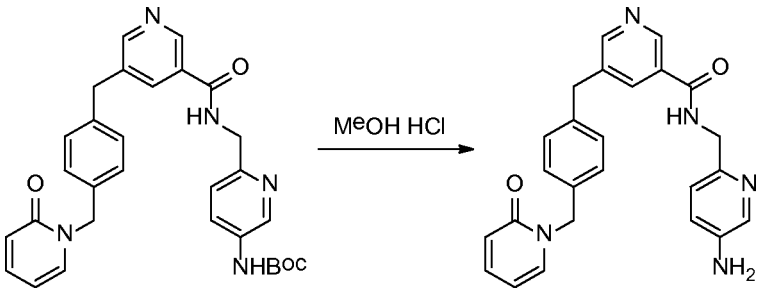
To the solution of 5-aminopicolinonitrile (500 mg, 4.2 mmol, 1.0 eq) in THF (10 mL) were added TEA (1.27 g, 12.6 mmol), DMAP (51.2 mg, 0.42 mmol), $(Boc)_2O$ (1.1 g, 5.04 mmol). The mixture was stirred at 60 °C for 2 h. After cooling to rt, 20 mL of H_2O was added, the mixture was extracted with EtOAc (3x30 mL); the organics were washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated, the residue was purified via silica column (PE/EtOAc = 3/1) to afford *tert*-butyl (6-cyanopyridin-3-yl)carbamate as a white solid (100 mg, 11%).



To a solution of *tert*-butyl (6-cyanopyridin-3-yl)carbamate (100 mg, 0.31 mmol, 1.0 eq) in MeOH.NH_3 (5 mL) was added Raney-nickel (50 mg). The mixture was stirred at rt under H_2 overnight. The mixture was filtered, the filtrate was concentrated to dryness to afford *tert*-butyl (6-(aminomethyl)pyridin-3-yl)carbamate as a yellow oil (90 mg, 88%).

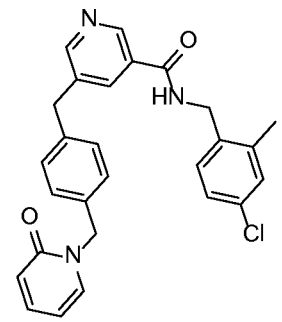


A mixture of *tert*-butyl (6-(aminomethyl)pyridin-3-yl)carbamate (90 mg, 0.28 mmol, 1.0 eq), 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (89 mg, 0.28 mmol, 1.0 eq), HATU (160 mg, 0.42 mmol, 1.5 eq) and TEA (85 mg, 0.84 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt overnight. The mixture was purified directly by flash chromatography to afford *tert*-butyl (6-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)pyridin-3-yl)carbamate as a colorless oil (60 mg, 41%).

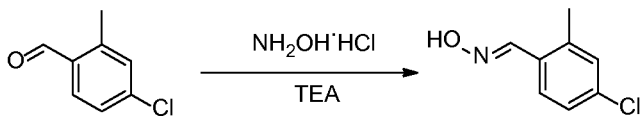


A mixture of tert-butyl (6-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)pyridin-3-yl)carbamate (60 mg, 0.11 mmol, 1.0 eq) in HCl/MeOH (25% w/w, 6mL) was stirred at rt overnight. The mixture was purified directly by flash chromatography to afford N-((5-aminopyridin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (25 mg, 52%). LRMS ($M+H^+$) m/z calculated 426.19, found 426.2. ^1H NMR (CD_3OD, 400 MHz) δ 9.12 (s, 1H), 8.86 (d, 2H), 7.98 (s, 1H), 7.82 (s, 1H), 7.60 (m, 2H), 7.27 (s, 4H), 6.79 (d, 2H), 6.72 (t, 1H), 5.25 (s, 2H), 4.64 (s, 2H), 4.22 (s, 2H).

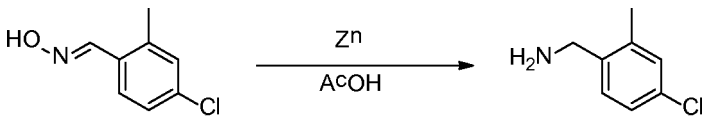
Example 86: Preparation of N-(4-chloro-2-methylbenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



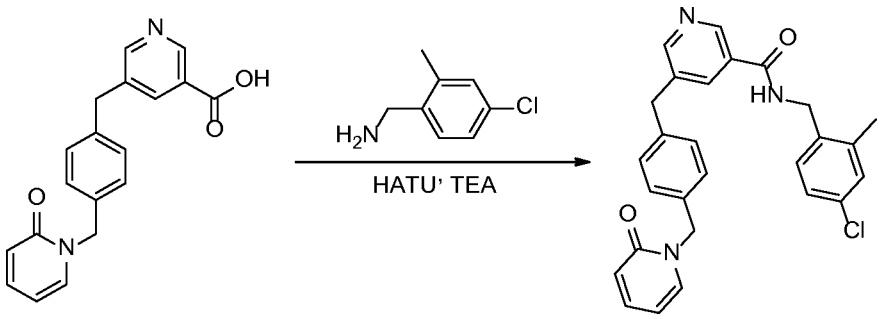
N-(4-chloro-2-methylbenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



To a solution of 4-chloro-2-methylbenzaldehyde (2 g, 12.94 mmol, 1 eq) in MeOH were added $NH_2OH.HCl$ (1.35 g, 19.41 mmol, 1.5 eq) and TEA (2.61 g, 25.88 mmol, 2 eq). The mixture was stirred at 60 °C for 3 h, and then concentrated, purified by flash chromatography to afford 4-chloro-2-methylbenzaldehyde oxime as a yellow solid (1.1 g, 50 %).

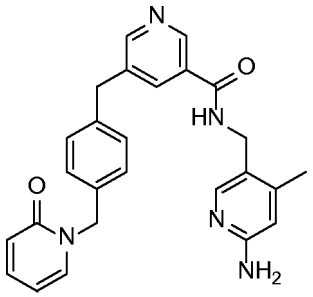


To a solution of 4-chloro-2-methylbenzaldehyde oxime (400 mg, 2.36 mmol, 1 eq) in AcOH was added Zn (1.5 g, 23.6 mmol, 10 eq). The mixture was stirred at 60 °C for 2 h. The mixture was neutralized with $NH_3.H_2O$, and extracted with EtOAc. The organics was concentrated to afford (4-chloro-2-methylphenyl)methanamine as a yellow oil (280 mg, 76 %).

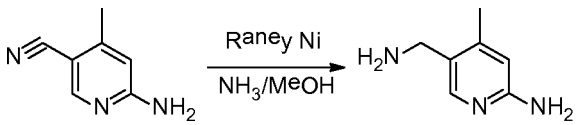


To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (150 mg, 0.468 mmol, 1 eq) in DMF were added HATU (267 mg, 0.702 mmol, 1.5 eq), TEA (95 mg, 0.936 mmol, 2 eq), (4-chloro-2-methylphenyl)methanamine (150 mg, 0.936 mmol, 2 eq). The mixture was stirred at rt for 5 h, poured into water and extracted with EtOAc. The organics was concentrated and purified by prep-HPLC to afford N-(4-chloro-2-methylbenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (80 mg, 37 %). LRMS ($M+H^+$) m/z calculated 458.2, found 458.2. ^1H NMR (d_6-DMSO, 400 MHz) δ 9.14-9.11 (m, 1 H), 8.91 (s, 1 H), 8.67 (s, 1 H), 8.12 (s, 1 H), 7.77-7.75 (m, 1 H), 7.42-7.38 (m, 1 H), 7.26-7.20 (m, 7 H), 6.40-6.38 (m, 1 H) , 6.23-6.20 (m, 1 H), 5.04 (s, 2 H), 4.43-4.42 (m, 2 H), 4.02 (s, 2 H), 2.08 (s, 3 H).

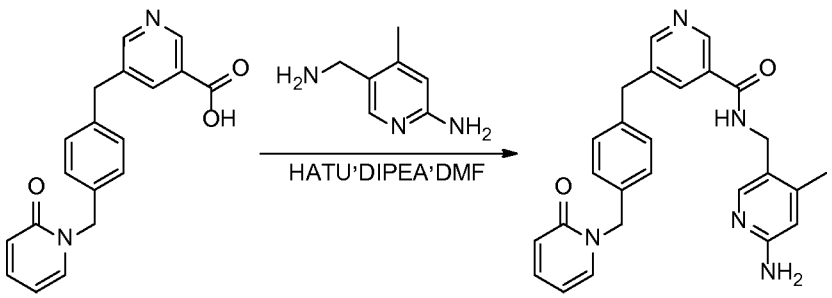
Example 87: Preparation of N-((6-amino-4-methylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



N-((6-amino-4-methylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

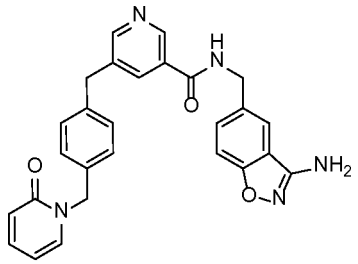


To a solution of 6-amino-4-methylnicotinonitrile (200 mg, 1.5 mmol, 1.0 eq) in NH_3/MeOH (5 mL) was added Raney Ni (about 20 mg). The suspension was hydrogenated at rt overnight. The mixture was filtered. The filtered cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography to afford 5-(aminomethyl)-4-methylpyridin-2-amine as a white solid (95 mg, 46%).

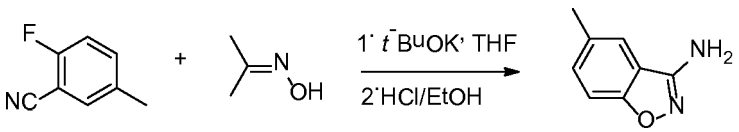


To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (100 mg, 0.31 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (120 mg, 0.93 mmol, 3.0 eq) and HATU (141 mg, 0.37 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, 5-(aminomethyl)-4-methylpyridin-2-amine (47 mg, 0.34 mmol, 1.1 eq) was then added and the mixture was stirred at rt for 2 h under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((6-amino-4-methylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (70 mg, 51%). LRMS ($M+H^+$) m/z caculated 440.2, found 440.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.90-8.75 (m, 2 H), 8.59 (d, 1 H), 8.01 (s, 1 H), 7.80-7.70 (m, 2 H), 7.45-7.35 (m, 1 H), 7.25-7.20 (m, 4 H), 6.39 (d, 1 H), 6.24 (s, 1 H), 6.21 (t, 1 H), 5.74 (s, 2 H), 5.04 (s, 2 H), 4.29 (d, 2 H), 3.98 (s, 2 H), 2.14 (s, 3 H).

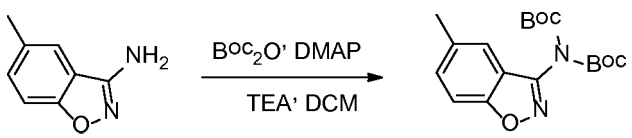
Example 88: Preparation of N-((3-aminobenzo[d]isoxazol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



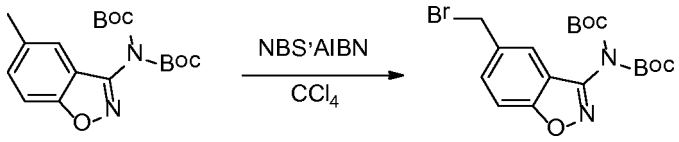
N-((3-aminobenzo[*d*]isoxazol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



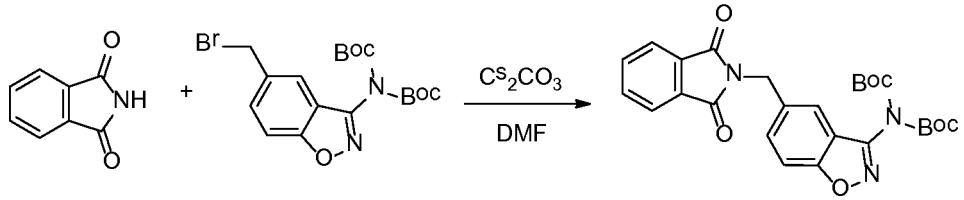
Potassium *tert*-butylate (4.57 g, 40.8 mmol, 1.1 eq.) was suspended in THF (40 mL). Acetone oxime (2.97 g, 40.7 mmol, 1.1 eq.) was added and the mixture was stirred at rt for 20 min., followed by the addition of a solution of 2-fluoro-5-methylbenzonitrile (5.00 g, 37 mmol, 1.0 eq.) in THF (30 mL) dropwise. The mixture was stirred at rt for 3 h and then refluxed overnight. The dark brown solution was quenched with water (10 mL). The mixture was partitioned between saturated $NaHCO_3$ aqueous solution (50 mL) and EA (150 mL). The aqueous layer was extracted with EA (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford brown oil. The crude oil was dissolved in EtOH (80 mL). H_2O (53 mL) and conc. HCl (27 mL) was added and the mixture was stirred at 90 °C for 2 h. Cooled to rt and the mixture was basified with NaOH aqueous solution to pH 10. The aqueous layer was extracted with EA (100 mL X3).The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography (PE/EA = 5/1, v/v) to afford 5-methylbenzo[d]isoxazol-3-amine as a white solid (2.5 g, 45.6%).



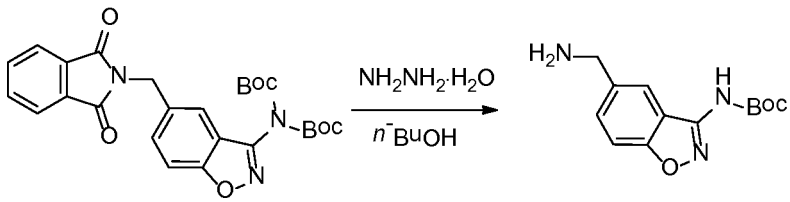
A mixture of 5-methylbenzo[d]isoxazol-3-amine (1.48 g, 10 mmol, 1.0 eq.), Boc_2O (6.54 g, 30 mmol, 3.0 eq.), DMAP (122 mg, 1.0 mmol, 0.1 eq.), TEA (4.2 mL, 30 mmol, 3.0eq.) in DCM (30 mL) was refluxed for 18 h. The mixture was washed with water (30 mL X 2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography (PE/EA/DCM = 1/20/1-1/7/1, v/v/v) to afford *tert*-butyl [(*tert*-butoxy)-N-(5-methylbenzo[d]isoxazol-3-yl)carbonylamino]formate as a white solid (3.2 g, 92%).



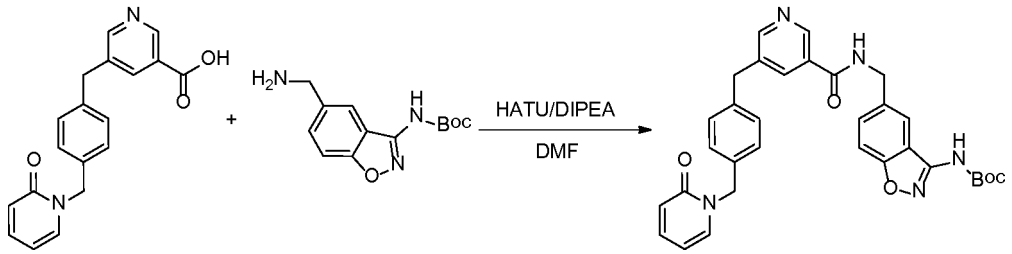
A mixture of tert-butyl [(tert-butoxy)-N-(5-methylbenzo[d]isoxazol-3-yl)carbonylamino]formate (1.04 g, 3 mmol, 1.0 eq.), NBS (536 mg, 3 mmol, 1.0 eq.), AIBN (53 mg, 0.32 mmol, 0.1 eq.) in CCl_4 (30 mL) was stirred at 85 °C for 5 h. Cooled to rt and the mixture was filtered. The filtrate was concentrated and the residue was purified via flash chromatography (PE/EA = 10/1, v/v) to afford tert-butyl {(*tert*-butoxy)-N-[5-(bromomethyl)benzo[d]isoxazol-3-yl]carbonylamino}formate as a white solid (970 mg, 75.8%).



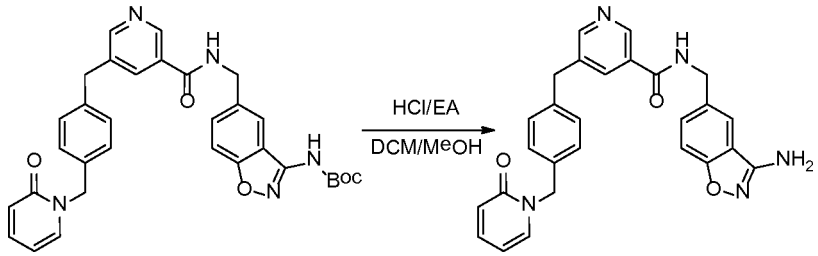
A mixture of *tert*-butyl {(*tert*-butoxy)-N-[5-(bromomethyl)benzo[d]isoxazol-3-yl]carbonylamino}formate (602 mg, 1.4 mmol, 1.0 eq.), isoindoline-1,3-dione (310 mg, 2.1 mmol, 1.5 eq.), Cs_2CO_3 (1.1 g, 3.4 mmol, 2.4 eq.) in DMF (10 mL) was stirred at 20 °C overnight. The mixture was partitioned between EA (20 mL) and water (20 mL). The aqueous layer was extracted with EA (20 mL X 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography (PE/EA = 5/1, v/v) to afford tert-butyl ((tert-butoxy)-N-{5-[(1,3-dioxobenzo[c]azolidin-2-yl)methyl]benzo[d]isoxazol-3-yl}carbonylamino)formate as a white solid (616 mg, 88.8%).



To a solution of *tert*-butyl ((tert-butoxy)-N-{5-[(1,3-dioxobenzo[c]azolidin-2-yl)methyl]benzo[d]isoxazol-3-yl}carbonylamino)formate (320 mg, 0.65 mmol, 1.0 eq.) in *n*-BuOH (10 mL) was added $NH_2NH_2.H_2O$ (0.20 mL). The mixture was stirred at rt overnight. The white slurry was diluted with DCM (10 mL) and filtered. The filtrate was evaporated and to the residue was triturated with Et_2O and dried to afford 3-(4-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid as a white solid (120 mg, 70.6%).

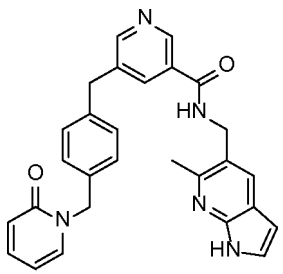


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (80 mg, 0.25 mmol, 1 eq), *tert*-butyl 5-(aminomethyl)benzo[d]isoxazol-3-ylcarbamate (66 mg, 0.25 mmol, 1.0 eq), HATU (114 mg, 0.30 mmol, 1.2 eq), DIPEA (0.5 mL) in DMF (3 mL) was stirred at rt overnight. The mixture was purified via prep-MPLC to afford *tert*-butyl 5-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)benzo[d]isoxazol-3-ylcarbamate as a white solid (96 mg, 67.8%).

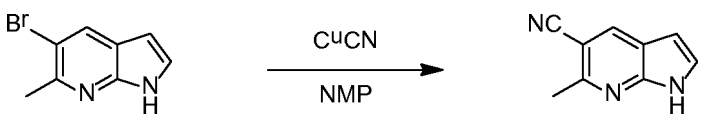


To a solution of *tert*-butyl 5-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)benzo[d]isoxazol-3-ylcarbamate (96 mg, 0.17 mmol, 1 eq.) in DCM/MeOH (v/v=1/1, 6 mL) was added HCl/EA (5 N, 3 mL) and the mixture was stirred at rt overnight. The precipitate was collected by suction and washed with EA and DCM to afford N-((3-aminobenzo[d]isoxazol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide HCl salt as a yellow solid (64 mg, 75.5%). LRMS ($M+H^+$) m/z calculated 466.2, found 466.2. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.18 (s, 1 H), 8.92 (s, 2 H), 7.91 (d, 1 H), 7.84 (s, 1 H), 7.72 (t, 1 H), 7.63 (d, 1 H), 7.41 (d, 1 H), 7.38-7.34 (m, 4 H), 6.74 (d, 1 H), 6.63 (t, 1 H), 5.28 (s, 2 H), 4.72 (s, 2 H), 4.31 (s, 2 H).

Example 89: Preparation of N-((6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

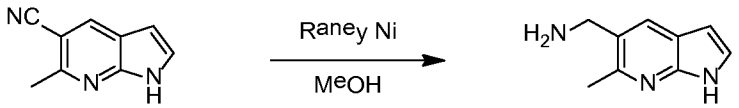


N-((6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

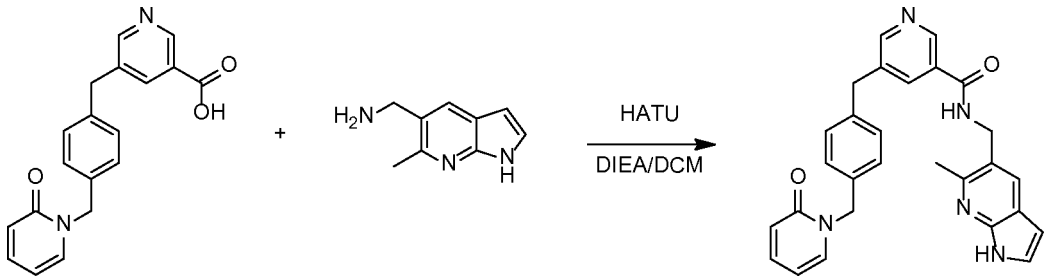


The mixture of 5-bromo-6-methyl-1H-pyrrolo[2,3-b]pyridine (2.11 g, 10.0 mmol, 1.0 eq) and CuCN (1.34 g, 15.0 mmol, 1.5 eq) in NMP (30 mL) was stirred at 170 °C for 6 h, then cooled, poured into 28% NH_4OH (100 mL), and extracted with EA (50 mL X2). The extracts were washed with water, brine, dried over anhydrous

sodium sulfate, filtered and concentrated to dryness to afford 6-methyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile as a brown solid (0.9 g, 62%).

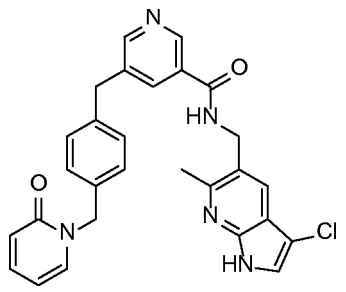


The mixture of 6-methyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (157 mg, 1.0 mmol, 1.0 eq) and Raney Ni in methanol (10 mL) and NH_3/MeOH (5 N, 5 mL) was hydrogenated overnight. The mixture was filtered through celite, rinsed with DCM/MeOH (10/1), and the filtrate was concentrated to dryness to afford (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine as a yellow solid (136 mg, 84%).

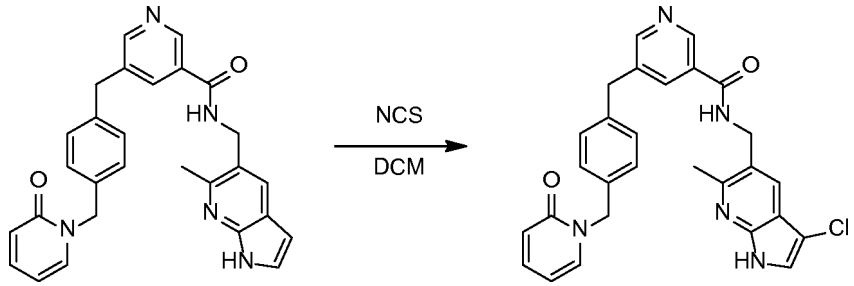


5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (135 mg, 0.42 mmol, 1.0 eq) and HATU (239 mg, 0.63 mmol, 1.5 eq) were mixed in DCM (5 mL) and DIEA (0.23 mL), and the mixture was stirred for 30 min, then (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine (68 mg, 0.42 mmolo, 1.0 eq) was added. The reaction mixture was stirred for 1 h, quenched with water. The DCM layer was washed with water, brine and dried with anhydrous sodium sulfate, purified via flash chromatography to afford N-((6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (70 mg, 35%). LRMS $(M+H)^+$ m/z calculated 464.2, found 464.2. ^{1}HNMR (CD_3OD, 400 MHz) δ 8.85 (s, 1 H), 8.57 (s, 1 H), 8.09 (s, 1 H), 7.93 (s, 1 H), 7.68 (d, 1 H), 7.52 (t, 1 H), 7.31-7.24 (m, 5 H), 6.57 (d, 1 H), 6.42 (d, 1 H), 6.38 (t, 1 H), 5.18 (s, 2 H), 4.69 (s, 2 H), 4.08 (s, 2 H), 2.64 (s, 3 H).

Example 90: Preparation of N-((3-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

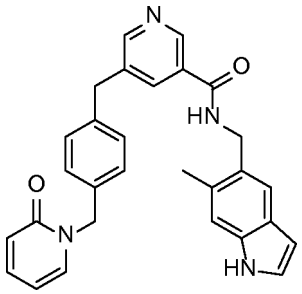


N-((3-chloro-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide

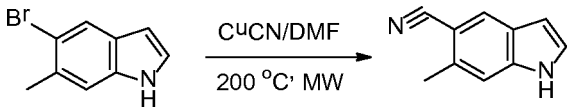


5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (135 mg, 0.42 mmol, 1.0 eq) and HATU (239 mg, 0.63 mmol, 1.5 eq) were mixed in DCM (5 mL) and DIEA (0.23 mL). The mixture was stirred for 30 min, then (6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine (68 mg, 0.42 mmolo, 1.0 eq) was added, and the reaction was stirred for 1 h. Then it was quenched with water, the DCM layer was washed with water, brine and dried with anhydrous sodium sulfate, and purified via flash chromatography to afford N-((6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (70 mg, 35%). LRMS $(M+H)^+$ m/z calculated 464.2, found 464.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.85 (s, 1 H), 8.57 (s, 1 H), 8.09 (s, 1 H), 7.93 (s, 1 H), 7.68 (d, 1 H), 7.52 (t, 1 H), 7.31-7.24 (m, 5 H), 6.57 (d, 1 H), 6.42 (d, 1 H), 6.38 (t, 1 H), 5.18 (s, 2 H), 4.69 (s, 2 H), 4.08 (s, 2 H), 2.64 (s, 3 H).

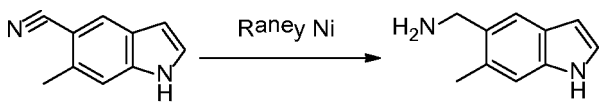
Example 91: Preparation of N-((6-methyl-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



N-((6-methyl-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide

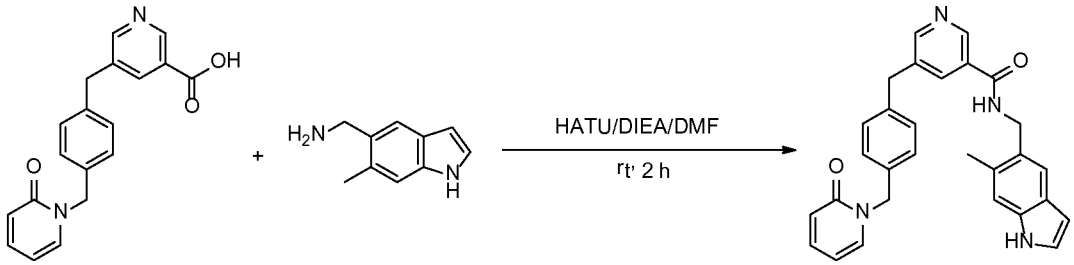


A mixture of 5-bromo-6-methyl-1H-indole (600 mg, 2.86 mmol, 1.0 eq) and CuCN (306 mg, 3.42 mmol, 1.2 eq) in NMP (10 mL) was stirred at 200 °C with microwave for 5 h. Then the mixture was poured into water (50 mL), extracted with EtOAc (50 mLx3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to afford 6-methyl-1H-indole-5-carbonitrile as a yellow solid (300 mg, 67%).



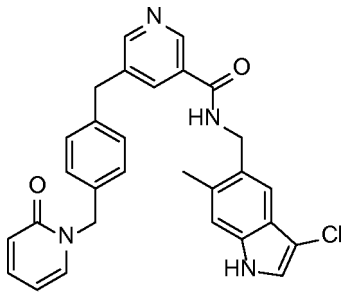
A mixture of 6-methyl-1H-indole-5-carbonitrile (120 mg, 0.77 mmol, 1.0 eq) and Raney Ni (50 mg) in methanol (15mL) was stirred at rt under H_2 atmosphere (1 atm) overnight. Then the mixture was filtered and

concentrated to afford (6-methyl-1H-indol-5-yl)methanamine as a yellow solid (120 mg, 97%). The solid was used for the next step without further purification.

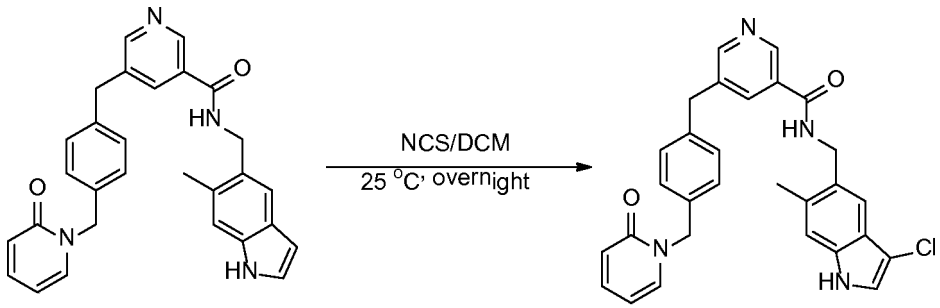


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (240 mg, 0.75 mmol, 1.0 eq), (6-methyl-1H-indol-5-yl)methanamine (120 mg, 0.75 mmol, 1.0 eq), HATU (570 mg, 1.5 mmol, 2.0 eq) and DIEA (290 mg, 2.25 mmol, 3.0 eq) in DMF (10 mL) was stirred at rt for 2 h. The mixture was poured into water (50 mL), extracted with EtOAc (50 mLx3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by pre-HPLC to afford N-((6-methyl-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamideas a yellow solid (150 mg, 43%). LRMS ($M+H^+$) m/z calculated 463.2, found 463.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.84 (s, 1 H), 8.56 (s, 1 H), 8.09 (s, 1 H), 7.68 (dd, 1 H), 7.53 (td, 1 H), 7.50 (s, 1 H), 7.29-7.23 (m, 5H), 7.16 (d, 1 H), 6.57 (d, 1 H), 6.40-6.37 (m, 2 H), 5.17 (s, 2 H), 4.66 (s, 2 H), 4.08 (s, 2 H), 2.44 (s, 3 H).

Example 92: Preparation of N-((3-chloro-6-methyl-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



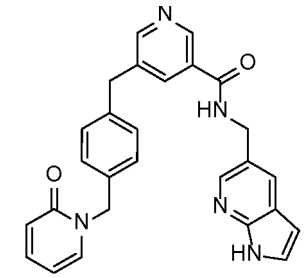
N-((3-chloro-6-methyl-1*H*-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



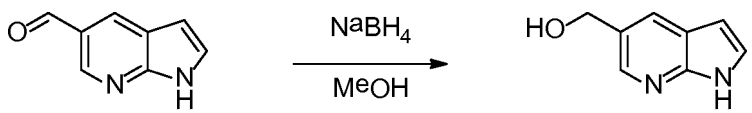
A mixture of N-((6-methyl-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (140 mg, 0.3 mmol, 1.0 eq) and NCS (40 mg, 0.3 mmol, 1.0 eq) in DCM (10 mL) was stirred at 25 °C overnight. Then the mixture was diluted with DCM (50 mL), washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to afford N-((3-chloro-6-methyl-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow

solid (15 mg, 10%). LRMS ($M+H^+$) m/z calculated 497.2, found 497.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.84 (s, 1 H), 8.56 (s, 1 H), 8.09 (s, 1 H), 7.68 (dd, 1 H), 7.53 (td, 1 H), 7.47 (s, 1 H), 7.29-7.24 (m, 5H), 7.17 (d, 1 H), 6.57 (d, 1 H), 6.38 (td, 1 H), 5.18 (s, 2 H), 4.69 (s, 2 H), 4.08 (s, 2 H), 2.46 (s, 3 H).

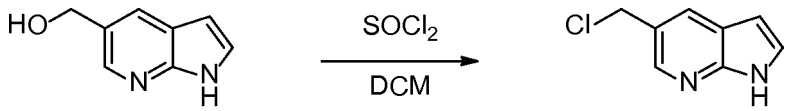
Example 93: Preparation of N-((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



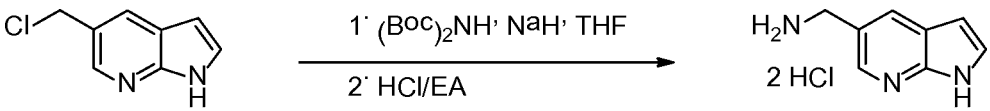
N-((1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



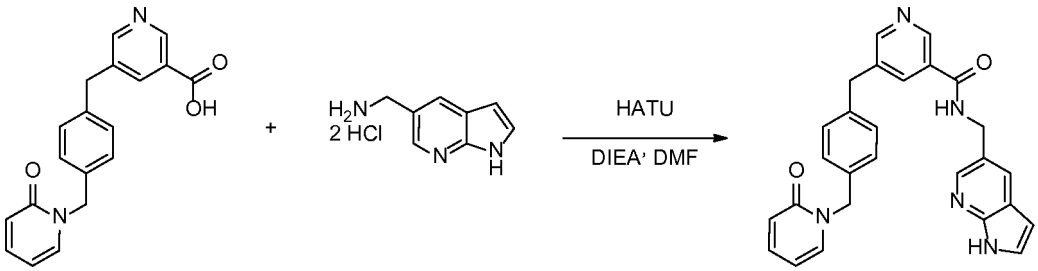
To the solution of 1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde (400 mg, 2.73 mmol, 1.0 eq) in MeOH (10 mL) was added sodium borohydride (208 mg, 5.46 mmol, 2.0 eq). The reaction was stirred for 1 h, and then purified via flash chromatography to afford (1H-pyrrolo[2,3-b]pyridin-5-yl)methanol as a white solid (310 mg, 76%).



To the suspension of (1H-pyrrolo[2,3-b]pyridin-5-yl)methanol (310 mg, 2.09 mmol, 1.0 eq) in dry DCM (10 mL) was added thionyl chloride (0.3 mL, 4.18 mmol, 2.0 eq) dropwise. The reaction was stirred for 3 h, and concentrated to dryness to afford 5-(chloromethyl)-1H-pyrrolo[2,3-b]pyridine as a white solid (420 mg, crude).

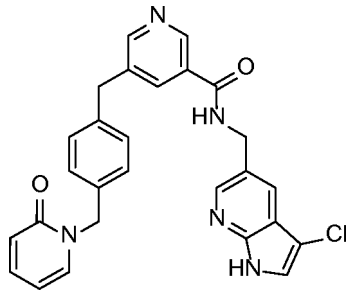


To the suspension of 5-(chloromethyl)-1H-pyrrolo[2,3-b]pyridine (420 mg, crude) in dry THF (15 mL) was added sodium hydride (130 mg, 60%, 3.2 mmol) followed by di-*tert*-butyl iminodicarboxylate (600 mg, 2.7 mmol, 1.1 eq). The reaction was stirred for 16 h, quenched with saturated aqueous ammonium chloride, and purified via flash chromatography to afford (1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine hydrochloeide as a white solid (190 mg, quant).

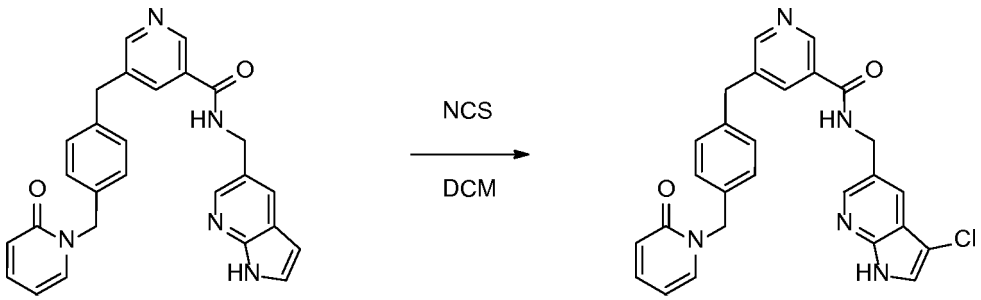


The mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (276 mg, 0.86 mmol, 1.0 eq) and HATU (495 mg, 1.30 mmol, 1.5 eq) in DMF (6 mL) and DIEA (1 mL) was stirred for 15 min. Then (1H-pyrrolo[2,3-b]pyridin-5-yl)methanamine hydrochloride (190 mg, 0.86 mmol, 1.0 eq) was added. The reaction was stirred for 1 h. The mixture was diluted with DCM (50 mL), washed with water, brine, and purified via flash chromatography to afford N-((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (290 mg, 75%). LRMS $(M+H)^+$ m/z calculated 450.2, found 450.2. ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.59 (s, 1 H), 9.19 (t, 1 H), 8.87 (d, 1 H), 8.61 (d, 1 H), 8.20 (d, 1 H), 8.03 (d, 1 H), 7.88 (d, 1 H), 7.74 (dd, 1 H), 7.46-7.36 (m, 2 H), 7.25-7.19 (m, 4 H), 6.42-6.37 (m, 2 H), 6.20 (t, 1 H), 5.03 (s, 2 H), 4.55 (d, 2 H), 3.99 (s, 2 H).

Example 94: Preparation of N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



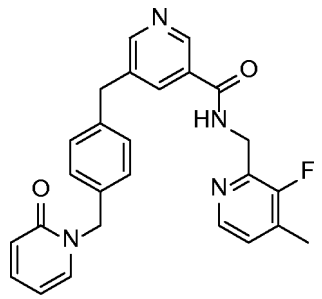
N-((3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



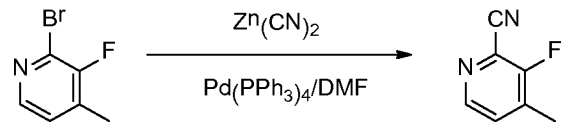
The suspension of N-((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (185 mg, 0.41 mmol, 1.0 eq) and NCS (55 mg, 0.41 mmol, 1.0 eq) in dry DCM (8 mL) was stirred at 25 °C for 8 h, and concentrated. Te residue was purified via flash chromatography to afford N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (100 mg, 50%). LRMS $(M+H)^+$ m/z calculated 484.2, found 484.2. ^{1}H NMR (DMSO-d6, 400 MHz) δ 11.96 (s, 1 H), 9.23 (t, 1 H), 8.87 (s, 1 H), 8.62 (s, 1 H), 8.30 (s, 1

H), 8.04 (s, 1 H), 7.87 (s, 1 H), 7.75 (d, 1 H), 7.68 (s, 1 H), 7.41 (t, 1 H), 7.24-7.20 (m, 4 H), 6.38 (d, 1 H), 6.20 (t, 1 H), 5.03 (s, 2 H), 5.00 (d, 2 H), 3.99 (s, 2 H).

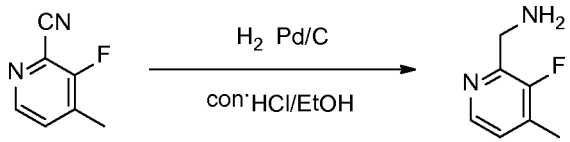
Example 95: Preparation of N-((3-fluoro-4-methylpyridin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



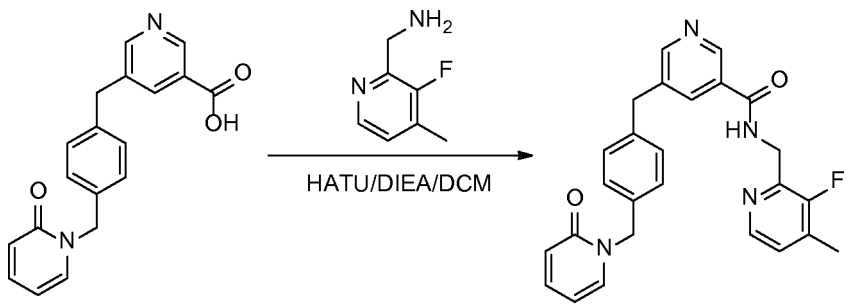
N-((3-fluoro-4-methylpyridin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



To a mixture of 2-bromo-3-fluoro-4-methylpyridine (2.0 g, 10.5 mmol, 1.0 eq) and zinc cyanide (1.23 g, 10.5 mmol, 1.0 eq) in DMF (30 mL) was added palladium tetra(triphenylphosphine) (607 mg, 0.52 mmol, 0.05 eq). The mixture was degassed and then heated to 90 °C for 3 h. After this time, the mixture was diluted with water (200 mL) and EtOAc (200 mL), filtered and the resulting layers were separated. The aqueous layer was further extracted with EtOAc (2x100 mL). The combined extracts were washed with water (200 mL), dried over $MgSO_4$, filtered and the solvent removed in vacuo. The resulting residue was purified by chromatograph on silica gel column (eluting with PE/EA = 20/1 to 6/1) to afford 3-fluoro-4-methylpicolinonitrile as a yellow oil (1.6 g, crude).

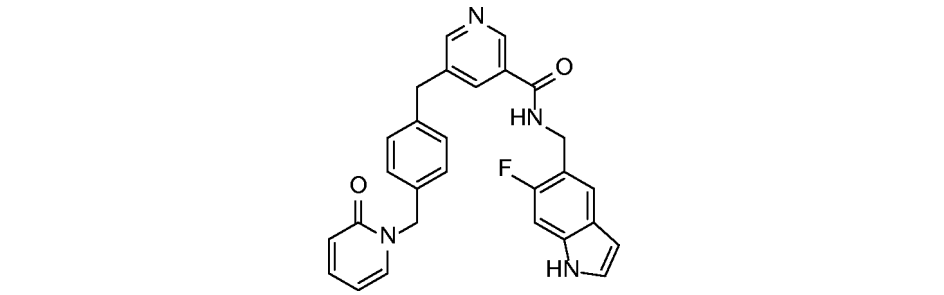


A stirred solution of 3-fluoro-4-methylpicolinonitrile (1.6 g, crude -30% purity, 1.0 eq) in 150 mL of ethanol and 6 mL (49 mmol) of conc HCl was hydrogenated (50 psi) over 300 mg of 10% Pd/C for 20 h. The catalyst was removed by filtration and the solvents removed under reduced pressure. The resulting solid was purified by flash chromatography (MeCN/H_2O = 1/19 to 2/3) to afford (3-fluoro-4-methylpyridin-2-yl)methanamine HCl salt as yellow solid (90 mg).

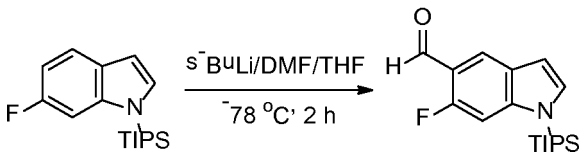


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (100 mg, 0.31 mmol, 1.0 eq), (3-fluoro-4-methylpyridin-2-yl)methanamine HCl salt (67 mg, 0.31 mmol, 1.0 eq), HATU (119 mg, 0.31 mmol, 1.0 eq) and DIEA (0.5 mL) in DCM (20 mL) was stirred at rt for 2 h. The mixture was evaporated under reduced pressure to give an oil, which was further purified by flash chromatography ($MeCN/H_2O$ = 1/9 to 1/1) to afford N-((3-fluoro-4-methylpyridin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (51 mg, 36%). LRMS ($M+H^+$) m/z calculated 443.1, found 443.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.15 (t, 1 H), 8.86 (d, 1 H), 8.62 (d, 1 H), 8.19 (d, 1 H), 8.03 (d, 1 H), 7.75 (dd, 1 H), 7.42-7.37 (m, 1 H), 7.29-7.19 (m, 5 H), 6.39 (d, 1 H), 6.22-6.19 (m, 1 H), 5.04 (s, 2 H), 4.60 (d, 2 H), 3.99 (s, 2 H), 2.28 (d, 3 H).

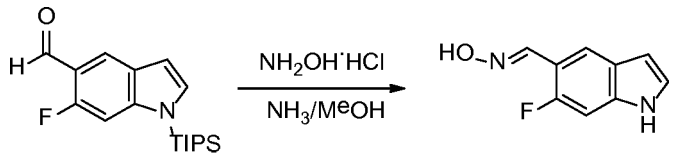
Example 96: Preparation of N-((6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



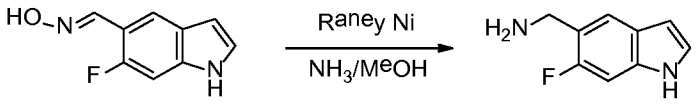
N-((6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



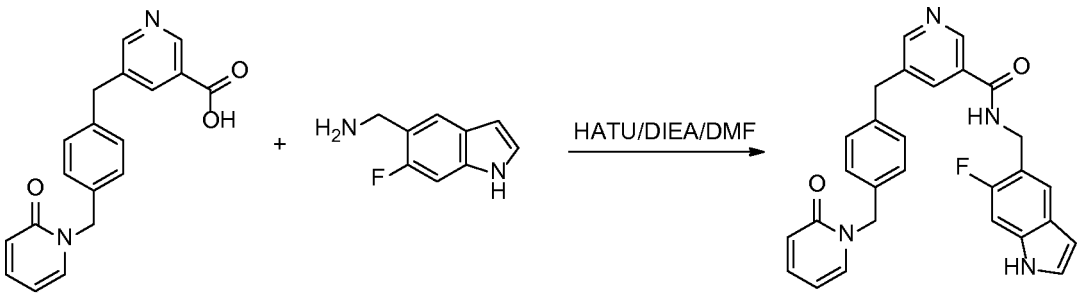
To a solution of 6-fluoro-1-(triisopropylsilyl)-1H-indole (2 g, 6.9 mmol, 1.0 eq) in THF (30 mL) was added *s*-BuLi (6.3 mL, 1.3 M, 1.2 eq) at -78 °C slowly. Then the mixture was stirred at this temperature for 1 h. DMF (1.5 g, 20.7 mmol, 3.0 eq) was added dropwise. The mixture was stirred at -78 °C for 1 h. Then the reaction was quenched by saturated aquoues NH_4Cl. The obtained mixture was extracted with EtOAc (50 mLx3). The organic layers were combined and washed with brine ,dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel column (PE/EtOAc = 100/1) to give 6-fluoro-1-(triisopropylsilyl)-1H-indole-5-carbaldehyde as a yellow oil (950 mg, 57%).



A mixture of 6-fluoro-1-(triisopropylsilyl)-1H-indole-5-carbaldehyde (780 mg, 2.45 mmol, 1.0 eq) and $NH_2OH.HCl$ (340 mg, 4.89 mmol, 2.0 eq) in NH_3/MeOH (15% w/w, 10 mL) was stirred at rt overnight. The mixture was concentrated. The residue was purified directly on silica gel column (PE/EtOAc = 50/1) to afford 6-fluoro-1H-indole-5-carbaldehyde oxime as a yellow solid (460 mg, crude).

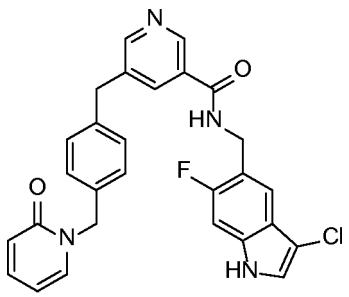


A mixture of 6-fluoro-1H-indole-5-carbaldehyde oxime (460 mg, 1.38 mmol, 1.0 eq) and Raney Ni (100 mg) in NH_3/MeOH (15% w/w, 10 mL) was stirred at rt under H_2 atmosphere (1 atm) overnight. Then the mixture was filtered and concentrated to afford (6-fluoro-1H-indol-5-yl)methanamine as a gray solid (420 mg, 95%). The solid was used for the next step without further purification.

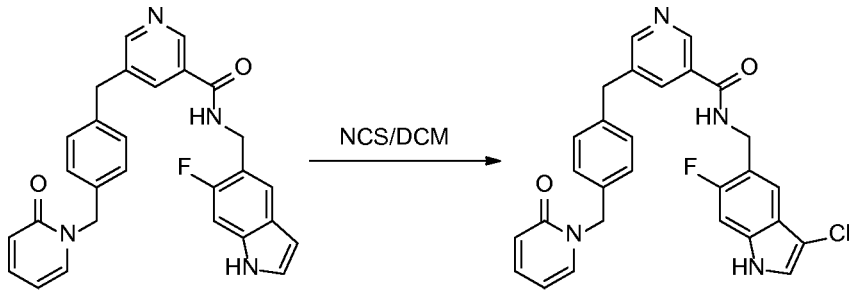


A mixture of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (312 mg, 0.98 mmol, 1.0 eq), (6-fluoro-1H-indol-5-yl)methanamine (160 mg, 0.98 mmol, 1.0 eq), HATU (559 mg, 1.47 mmol, 1.5 eq) and DIEA (379 mg, 2.94 mmol, 3.0 eq) in DMF (8 mL) was stirred at rt for 2 h. The mixture was purified directly by flash chromatography to afford N-((6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow solid (100 mg, 22%). LRMS ($M+H^+$) m/z calculated 467.19, found 467.2. ^1H NMR (CD_3OD, 300 MHz) δ 8.84 (s, 1 H), 8.55 (s, 1 H), 8.09 (s, 1 H), 7.68 (dd, 1 H), 7.56-7.50 (m, 2 H), 7.29-7.22 (m, 5 H), 7.11 (d, 1 H), 6.57 (d, 1 H), 6.43 (d, 1 H), 6.38 (td, 1 H), 5.18 (s, 2 H), 4.69 (s, 2 H), 4.07 (s, 2 H).

Example 97: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



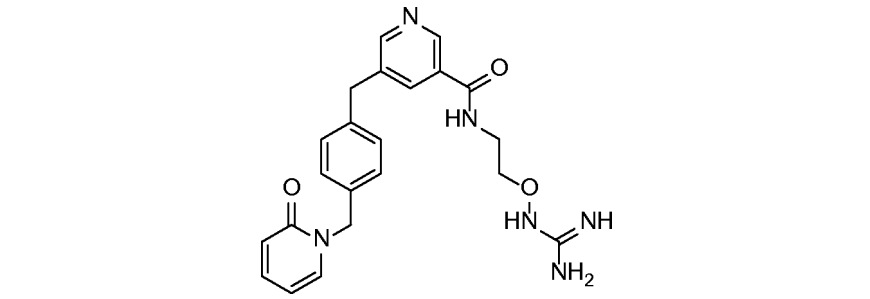
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



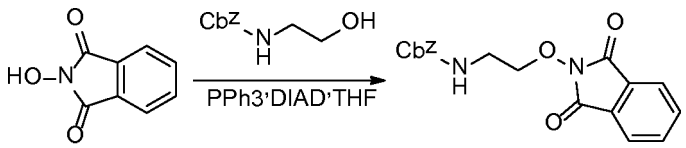
A solution of N-((6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (68 mg, 0.15 mmol, 1.0 eq) and NCS (39 mg, 0.29 mmol, 2.0 eq) in DCM (10 mL) was stirred at 20 °C

overnight. Then the mixture was purified by flash chromatography to give N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a yellow oil (8.1 mg, 11%). LRMS ($M+H^+$) m/z calculated 501.2, found 501.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.85 (s, 1 H), 8.57 (s, 1 H), 8.09 (s, 1 H), 7.67 (dd, 1 H), 7.55-7.51 (m, 2 H), 7.30-7.24 (m, 5 H), 7.14 (d, 1 H), 6.57 (d, 1 H), 6.39 (td, 1 H), 5.18 (s, 2 H), 4.71 (s, 2 H), 4.09 (s, 2 H).

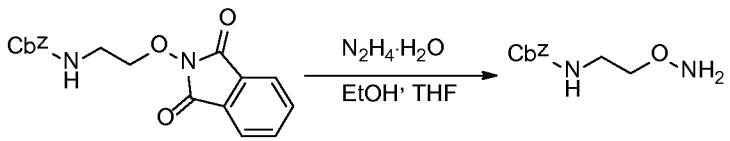
Example 98: Preparation of N-(2-(guanidinooxy)ethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



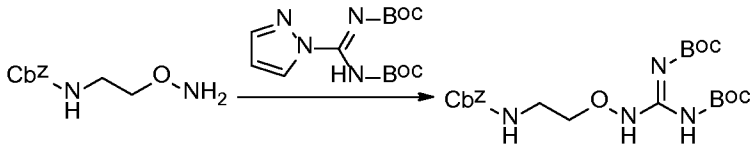
N-(2-(guanidinooxy)ethyl)-5-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)nicotinamide



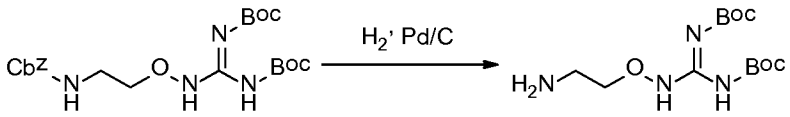
To a solution of 2-hydroxyisoindoline-1,3-dione (4.9 g, 30 mmol, 1.0 eq), benzyl (2-hydroxyethyl)carbamate (5.9 g, 30 mmol, 1.0 eq) and PPh_3 (7.9 g, 30 mmol, 1.0 eq) in THF (100 mL) was added DIAD (6.1 g, 30 mmol, 1.0 eq). The mixture was stirred at rt overnight under N_2. The reaction was mixed with saturated $NaHCO_3$ (100 mL) and extracted with EA (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (DCM/MeOH = 400/1 to 100/1) to afford benzyl (2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)carbamate as a yellow solid (7.0 g, 69%).



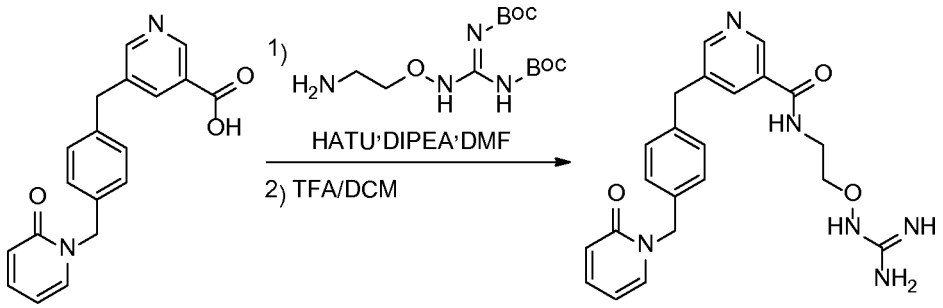
To a solution of benzyl (2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)carbamate (6.0 g, 17.7 mmol, 1.0 eq) in EtOH (60 mL) and THF (60 mL) was added $N_2H_4.H_2O$ (8.8 g, 177 mmol, 10.0 eq). The mixture was stirred at rt for 2 h. The mixture was concentrated to dryness under reduced pressure. The residue was added DCM (100 mL) and stirred for 1 h. The suspension was filtered. The filtrate was concentrated to dryness under reduced pressure. The residue was purified via silica gel column (DCM/MeOH = 100/1 to 50/1) to afford benzyl (2-(aminooxy)ethyl)carbamate as a colorless oil (3.7 g, 85%).



To a solution of benzyl (2-(aminooxy)ethyl)carbamate (3.7 g, 17.6 mmol, 1.0 eq) in DMF (50 mL) was added *tert*-butyl (((*tert*-butoxycarbonyl)amino)(1H-pyrazol-1-yl)methylene)carbamate (5.5 g, 17.6 mmol, 1.0 eq). The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was purified via silica gel column (PE/EA = 20/1 to DCM/MeOH = 300/1) to afford (N,N'-Di(*tert*-butoxycarbonyl))2-(benzyloxycarbonylamino)ethoxyguanidine as a colorless oil (1.2 g, 15%).

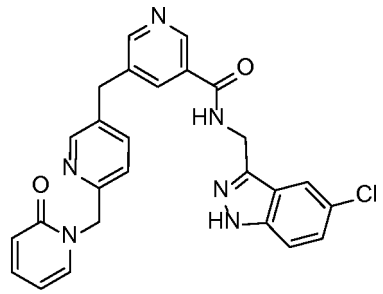


To a solution of (N,N'-Di(*tert*-butoxycarbonyl))2-(benzyloxycarbonylamino)ethoxyguanidine (1.2 g, 2.66 mmol, 1.0 eq) in EtOH (20 mL) and THF (20 mL) was added Pd/C (120 mg, 10% Pd). The mixture was hydrogenated at rt for 1 h. The mixture was filtered. The filtrate was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford (N,N'-Di(*tert*-butoxycarbonyl))2-(amino)ethoxyguanidine as a white solid (320 mg, 38%).

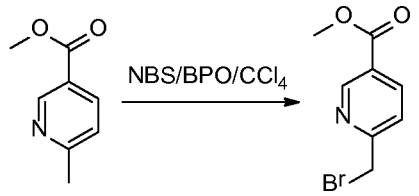


To a solution of 5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinic acid (60 mg, 0.19 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (73 mg, 0.57 mmol, 3.0 eq) and HATU (86 mg, 0.23 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (N,N'-di(*tert*-butoxycarbonyl))2-(amino)ethoxyguanidine (60 mg, 0.19 mmol, 1.0 eq) was then added and the mixture was stirred at rt overnight under N_2. The reaction was purified via flash chromatography to afford the coupling product as a white solid (75 mg, 64%). To a solution of above product (75 mg, 0.12 mmol, 1.0 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (5 mL), neutralized with saturated $NaHCO_3$ (5 mL) and concentrated. The residue was purified via Prep-HPLC to afford N-(2-(guanidinooxy)ethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (20 mg, 40%). LRMS ($M+H^+$) m/z caculated 421.2, found 421.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.20 (d, 1 H), 8.64 (t, 1 H), 8.61 (d, 1 H), 7.99 (t, 1 H), 7.76 (dd, 1 H), 7.45-7.35 (m, 1 H), 7.30-7.20 (m, 4 H), 6.39 (d, 1 H), 6.21 (td, 1 H), 5.11 (brs, 2 H), 5.04 (s, 2 H), 4.38 (brs, 2 H), 3.99 (s, 2 H), 3.70 (t, 2 H), 3.50-3.40 (m, 2 H).

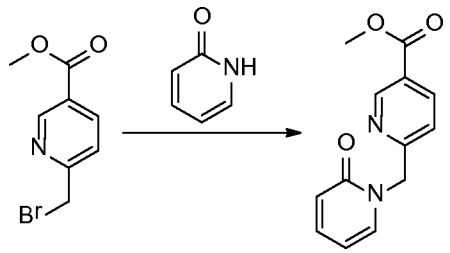
Example 99: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide



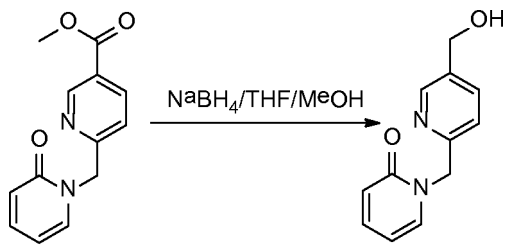
N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamide



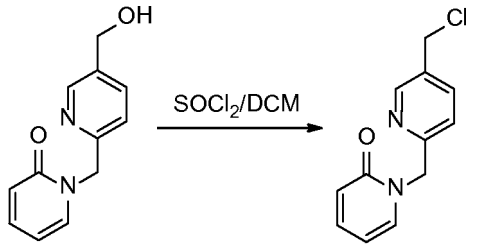
A mixture of methyl 6-methylnicotinate (2 g, 13.2 mmol, 1.0 eq), NBS (2.4 g, 13.2 mmol, 1.0 eq) and BPO (319 mg, 1.32 mmol, 0.1 eq) in CCl_4 (40 mL) was stirred at 95 °C under N_2 overnight. Then the reaction was quenched with water (10 mL), extracted with DCM (50 mLx3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (PE/EtOAc = 20/1) to afford methyl 6-(bromomethyl)nicotinate as a yellow solid (780 mg, 26%).



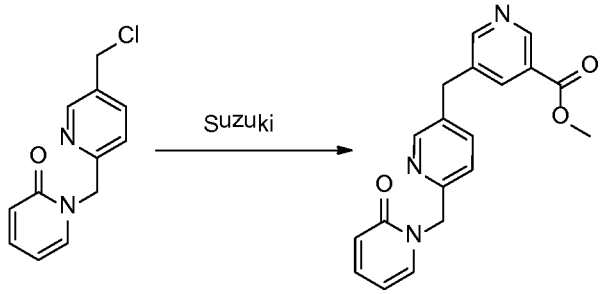
A mixture of methyl 6-(bromomethyl)nicotinate (880 mg, 3.83 mmol, 1.0 eq), pyridin-2(1H)-one (545 mg, 5.74 mmol, 1.5 eq) and K_2CO_3 (1.06 g, 7.66 mmol, 2.0 eq) in CH_3CN (30 mL) was stirred at 85 °C overnight. After cooled to rt, the mixture was filtered. The filtrate was concentrated. The residue was purified by flash chromatography to afford methyl 6-((2-oxopyridin-1(2H)-yl)methyl)nicotinate as a yellow solid (730 mg, 78%).



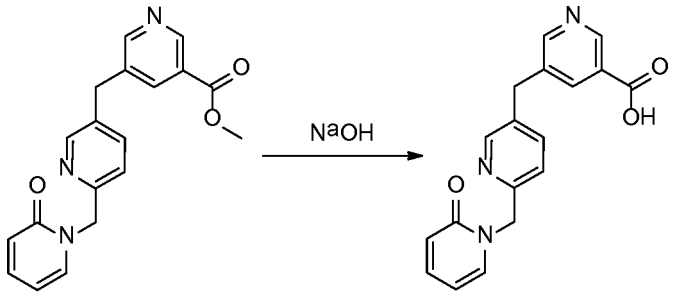
The solution of methyl 6-((2-oxopyridin-1(2H)-yl)methyl)nicotinate (1.15 g, 4.7 mmol, 1.0 eq) in THF (30 mL) was heated to reflux. Then MeOH was added slowly. The mixture was refluxed and stirred for 2 h. LCMS showed the reaction was completed. Then the mixture was cooled to rt and water (10 mL) was added. The obtained mixture was concentrated and the residue was diluted with MeOH (50 mL), filtered and the filtrate was concentrated to give 1-((5-(hydroxymethyl)pyridin-2-yl)methyl)pyridin-2(1H)-one as a yellow solid (1.15 g, quant). The solid was used for the next step without further purification.



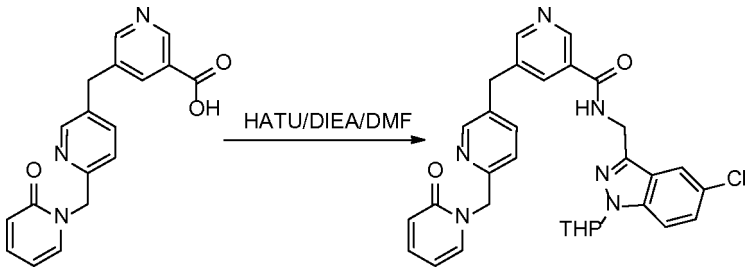
The mixture of 1-((5-(hydroxymethyl)pyridin-2-yl)methyl)pyridin-2(1H)-one (1.15 g, 5.3 mmol, 1.0 eq) in DCM (20 mL) and $SOCl_2$ (10 mL) was stirred at rt overnight. Then the mixture was concentrated to give 1-((5-(chloromethyl)pyridin-2-yl)methyl)pyridin-2(1H)-one as a yellow solid (1.1 g, 92%).



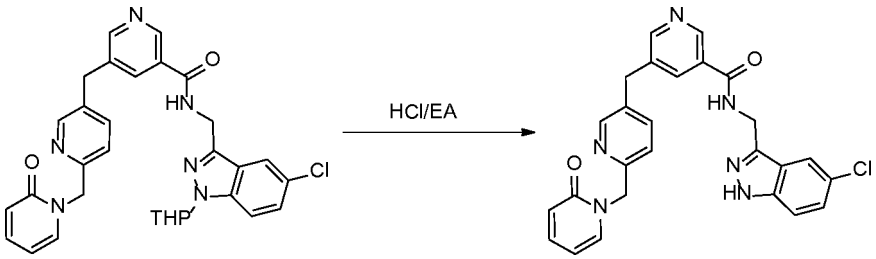
The mixture of ethyl 5-bromonicotinate (1 g, 4.3 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1 g, 4.3 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (157 mg, 0.05 eq) and KOAc (1.26 g, 12.9 mmol, 3.0 eq) in dioxane (30 mL) was degassed with N_2 and stirred at 85 °C overnight. Then the mixture was cooled, 1-((5-(chloromethyl)pyridin-2-yl)methyl)pyridin-2(1H)-one (1.02 g, 4.3 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (157 mg, 0.05 eq) and an aqueous solution of Na_2CO_3 (1.37 g, 12.9 mmol, 3.0 eq) in 10 mL of water were added. The mixture was degassed with N_2 and stirred at 95 °C for 2 h. Then the mixture was cooled and concentrated, the residue was dissolved in EtOAc (150 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via silica gel column (PE/EtOAc = 1/1-quant EtOAc) to afford methyl 5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinate as a brown solid (620 mg, 41%).



The solution of methyl 5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinate (620 mg, 1.78 mmol, 1.0 eq) in MeOH (5 mL) was treated with an aqueous solution of NaOH (213 mg, 5.33 mmol, 3.0 eq) in 10 mL of water. The mixture was stirred for 2 h at rt. Then the mixture was concentrated and the residue was acidified with 2 N HCl till pH 3. The mixture was concentrated to give 5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinic acid as a gray solid (1.0 g, quant). The solid was used for the next step without further purification.

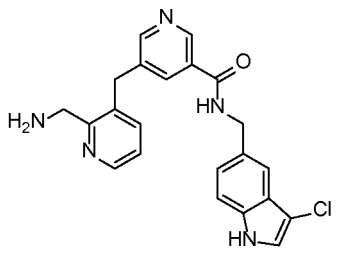


A mixture of (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (200 mg, 0.75 mmol, 1.0 eq), 5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinic acid (242 mg, 0.75 mmol, 1.0 eq), HATU (428 mg, 1.13 mmol, 1.5 eq) and DIEA (290 mg, 2.25 mmol, 3.0 eq) in DMF (10 mL) was stirred at rt for 2 h. The mixture was poured into water (50 mL). The appeared solid was filtered and dried to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide as a gray solid (200 mg, 47%). The solid was used for the next step without further purification.

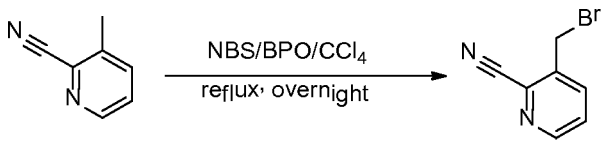


The solutuion of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide (200 mg, 0.35 mmol, 1.0 eq) in 1 N HCl/EtOAc (8 mL) and MeOH (1 mL) was stirred at rt for 2 h. Then the mixture was concentrated and the residue was washed with MeOH to give N-((5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide HCl salt as a white solid (97.6 mg, 58%). LRMS ($M+H^+$) m/z calculated 485.1, found 485.1. ^1H NMR (DMSO-d6, 400 MHz) δ 13.21 (brs, 1 H), 9.62 (t, 1 H), 9.09 (s, 1 H), 8.91 (s, 1 H), 8.70 (s, 1 H), 8.58 (s, 1 H), 8.01 (d, 1 H), 7.94 (s, 1 H), 7.85 (d, 1 H), 7.54 (d, 1 H), 7.47 (t, 1 H), 7.35 (t, 2 H), 6.40 (d, 1 H), 6.29 (t, 1 H), 5.26 (s, 2 H), 4.80 (d, 2 H), 4.23 (s, 2 H).

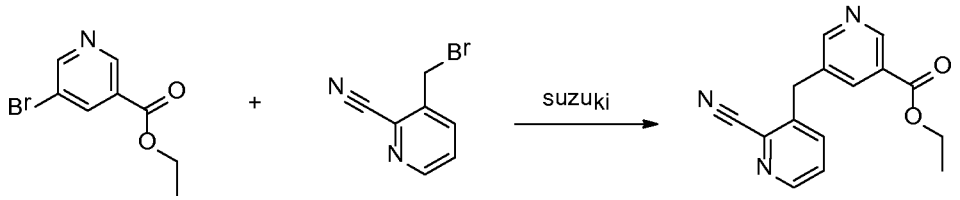
Example 100: Preparation of 5-((2-(aminomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



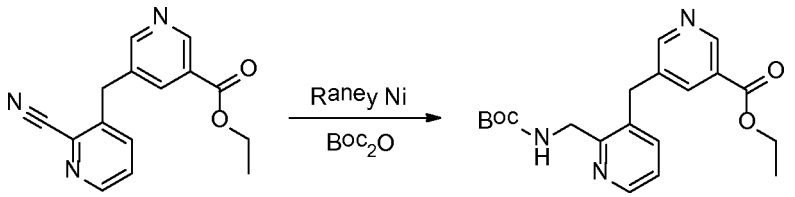
5-((2-(aminomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



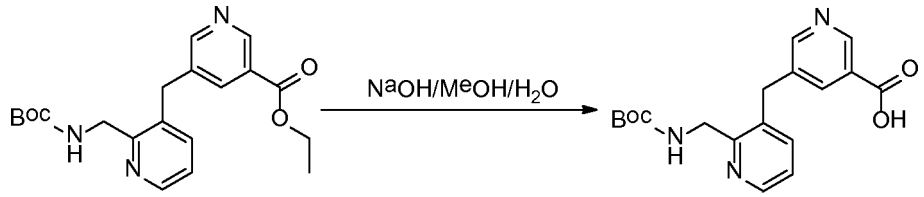
A mixture of 3-methylpicolinonitrile (2 g, 16.9 mmol, 1.0 eq), NBS (3 g, 16.9 mmol, 1.0 eq) and BPO (411 mg, 1.7 mmol, 0.1 eq) in CCl_4 (30 mL) was refluxed and stirred overnight. Then the mixture was cooled to rt and concentrated. The residue was diluted with water (50 mL), extracted with DCM (50 mLx3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (PE/EtOAc = 5/1) to afford 3-(bromomethyl)picolinonitrile as a brown solid (2.1 g, 63%).



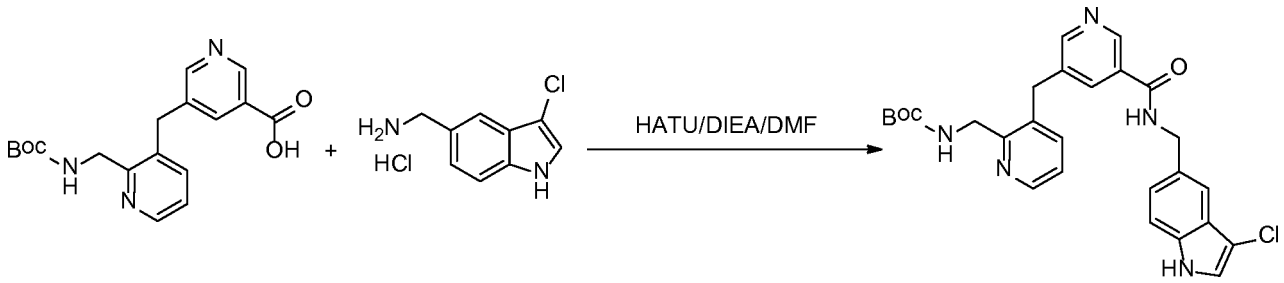
The mixture of ethyl 5-bromonicotinate (1 g, 4.34 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1g, 4.34 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (157 mg, 5%) and KOAc (1.27 g, 13 mmol, 3.0 eq) in dioxane (36 mL) was degassed with N_2 and stirred at 85 °C overnight. After cooling to rt, 3-(bromomethyl)picolinonitrile (0.85 g, 4.34 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (157 mg, 5%) and an aqueous solution of Na_2CO_3 (1.38 g, 13 mmol, 3.0 eq) in 10 mL of water were added. The mixture was degassed with N_2 and stirred at 95 °C for 2 h. Then the mixture was concentrated. The residue was diluted with EtOAc (100 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via silica flash chromatography (PE/EtOAc = 1/1) to afford ethyl 5-((2-cyanopyridin-3-yl)methyl)nicotinate as a yellow solid (340 mg, 29%).



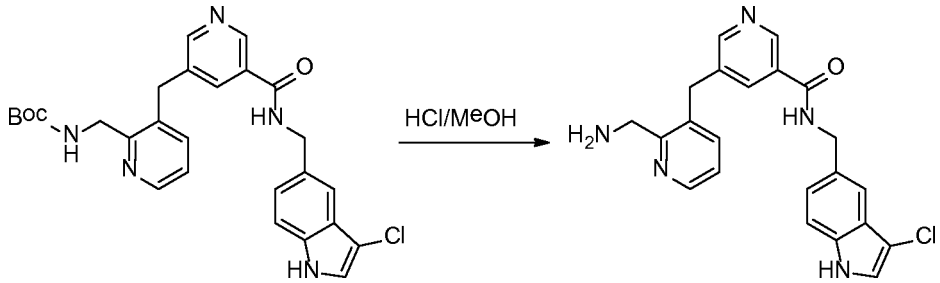
A mixture of ethyl 5-((2-cyanopyridin-3-yl)methyl)nicotinate (340 mg, 0.93 mmol, 1.0 eq), Boc_2O (202 mg, 1.02 mmol, 1.1 eq) and Raney Ni (50 mg) in methanol (20 mL) was stirred at rt under H_2 atmosphere (1 atm) for 5 h. Then the mixture was filtered and concentrated. The residue was purified via silica gel column (PE/EtOAc = 5/1) to afford ethyl 5-((2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-3-yl)methyl)nicotinate as a yellow oil (300 mg, 87%).



To a solution of ethyl 5-((2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-3-yl)methyl)nicotinate (300 mg, 0.8 mmol, 1.0 eq) in MeOH (5 mL) and H_2O (5 mL) was added NaOH (65 mg, 1.6 mmol, 2.0 eq). The mixture was stirred at rt for 2 h. Then the organic solvents were evaporated. To the residue was added conc. HCl till pH 2. The obtained mixture was concentrated to afford 5-((2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-3-yl)methyl)nicotinic acid as a yellow solid (470 mg, crude, contained NaCl).

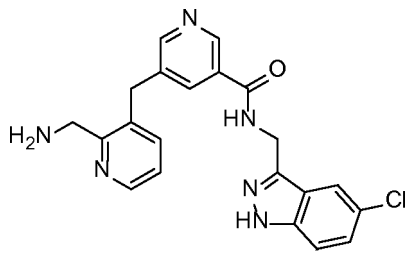


A mixture of 5-((2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-3-yl)methyl)nicotinic acid (235 mg, crude, 0.4 mmol, 1.0 eq), (3-chloro-1H-indol-5-yl)methanamine HCl salt (95 mg, 0.44 mmol, 1.1 eq), HATU (228 mg, 0.6 mmol,1.5 eq) and DIEA (258 mg, 2.0 mmol, 5.0 eq) in DMF (10 mL) was stirred at rt overnight. The mixture was purified directly by flash chromatography to afford *tert*-butyl ((3-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)pyridin-2-yl)methyl)carbamate as a yellow solid (95 mg, 47%).

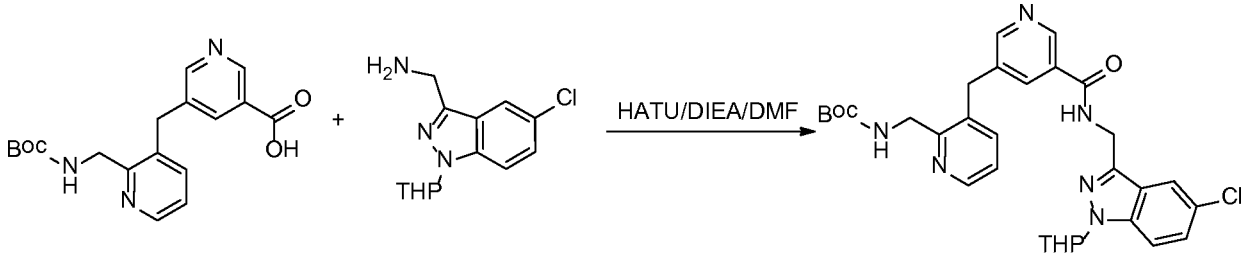


A mixture of *tert*-butyl ((3-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)pyridin-2-yl)methyl)carbamate (95 mg, 0.19 mmol, 1.0 eq) in HCl/MeOH (20% w/w, 10 mL) was stirred at rt for 2 h. The mixture was purified directly by flash chromatography to afford 5-((2-(aminomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide as a yellow solid (12 mg, 16%). LRMS ($M+H^+$) m/z calculated 406.14, found 406.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.89 (s, 1 H), 8.54 (s, 1 H), 8.46 (s, 1 H), 8.01 (s, 1 H), 7.57 (d, 1 H), 7.51 (s, 1 H), 7.35 (d, 1 H), 7.29-7.19 (m, 3 H), 4.66 (s, 2 H), 4.15 (s, 2 H), 3.89 (s, 2 H).

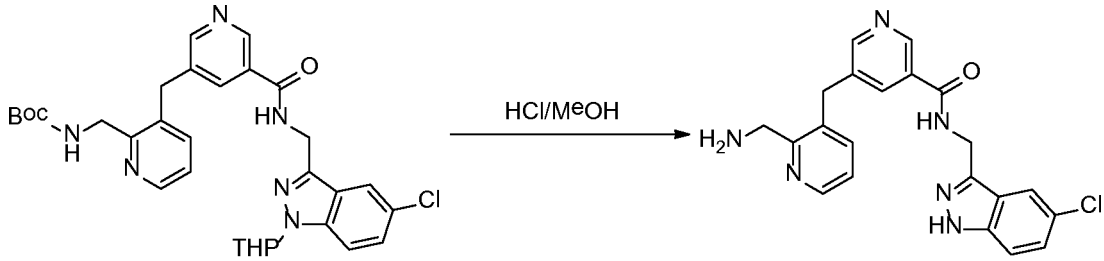
Example 101: Preparation of 5-((2-(aminomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide



5-((2-(aminomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide

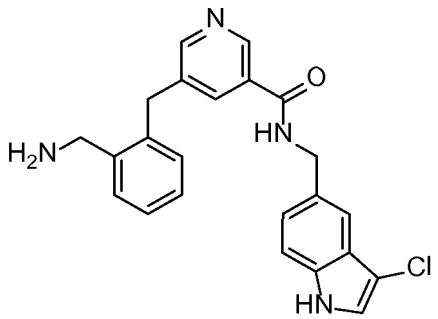


A mixture of 5-((2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-3-yl)methyl)nicotinic acid (235 mg, crude, 0.4 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (117 mg, 0.44 mmol, 1.1 eq), HATU (228 mg, 0.6 mmol,1.5 eq) and DIEA (155 mg, 1.2 mmol, 3.0 eq) in DMF (10 mL) was stirred at rt overnight. The mixture was purified directly by flash chromatography to afford *tert*-butyl ((3-((5-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)pyridin-2-yl)methyl)carbamate as a yellow solid (132 mg, 56%).

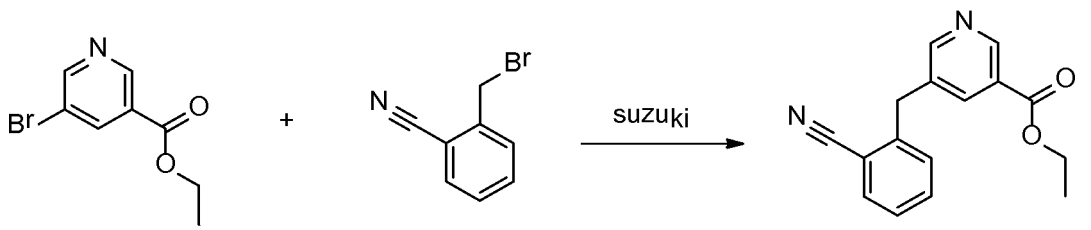


A mixture of *tert*-butyl ((3-((5-(((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)pyridin-2-yl)methyl)carbamate (132 mg, 0.22 mmol, 1.0 eq) in HCl/MeOH (20% w/w, 10 mL) was stirred at rt for 2 h. The mixture was purified directly by flash chromatography to afford 5-((2-(aminomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide as a yellow solid (14 mg, 16%). LRMS ($M+H^+$) m/z calculated 407.14, found 407.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.87 (s, 1 H), 8.56 (s, 1 H), 8.46 (d, 1 H), 8.01 (s, 1 H), 7.85 (s, 1 H), 7.59 (d, 1 H), 7.48 (d, 1 H), 7.34 (dd, 1 H), 7.30-7.27 (m, 1 H), 4.18 (s, 2 H), 3.89 (s, 2 H), 3.35 (s, 2 H).

Example 102: Preparation of 5-(2-(aminomethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide

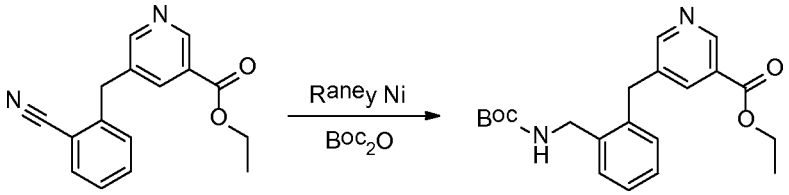


5-(2-(aminomethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide

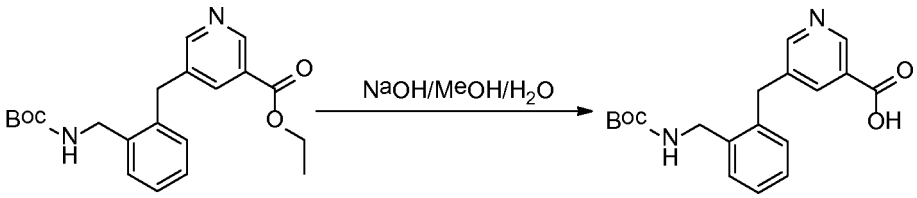


The mixture of ethyl 5-bromonicotinate (1 g, 4.34 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1g, 4.34 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (157 mg, 5%) and KOAc (1.27 g, 13 mmol, 3.0 eq) in dioxane (36 mL) was degassed with N_2 and stirred at 85 °C overnight. After cooling to rt, 2-(bromomethyl)benzonitrile (0.85 g, 4.34 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (157 mg, 5%) and an aqueous solution of Na_2CO_3 (1.38 g, 13 mmol, 3.0 eq) in 10 mL of water were added. The mixture was degassed with N_2 and

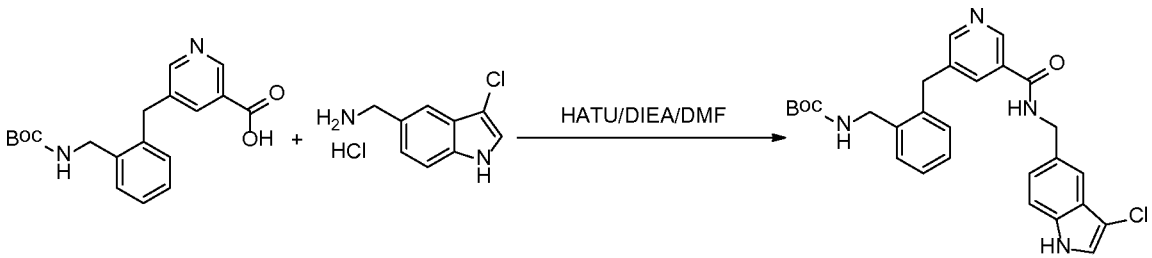
stirred at 95 °C for 2 h. Then the mixture was concentrated. The residue was diluted with EtOAc (100 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via silica flash chromatography (PE/EtOAc = 5/1) to afford ethyl 5-(2-cyanobenzyl)nicotinate as a yellow oil (750 mg, 65%).



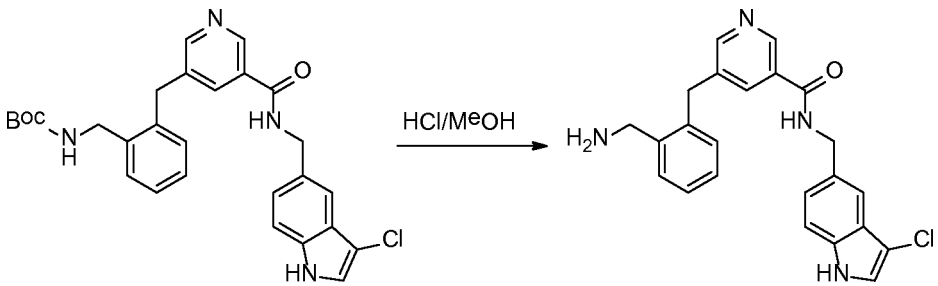
A mixture of ethyl 5-(2-cyanobenzyl)nicotinate (750 mg, 2.8 mmol, 1.0 eq), Boc_2O (676 mg, 3.1 mmol, 1.1 eq) and Raney Ni (100 mg) in methanol (20 mL) was stirred at rt under H_2 atmosphere (1 atm) overnight. Then the mixture was filtered and concentrated. The residue was purified via silica gel column (PE/EtOAc = 5/1) to afford ethyl 5-(2-(((tert-butoxycarbonyl)amino)methyl)benzyl)nicotinate as a yellow oil (520 mg, 50%).



To a solution of ethyl 5-(2-(((*tert*-butoxycarbonyl)amino)methyl)benzyl)nicotinate (350 mg, 0.95 mmol, 1.0 eq) in MeOH (5 mL) and H_2O (5 mL) was added NaOH (76 mg, 1.89 mmol, 2.0 eq). The mixture was stirred at rt for 1 h. Then the organic solvents were evaporated. To the residue was added conc. HCl till pH 2. The obtained mixture was concentrated to afford 5-(2-(((*tert*-butoxycarbonyl)amino)methyl)benzyl)nicotinic acid as a yellow solid (500 mg, crude, contained NaCl).

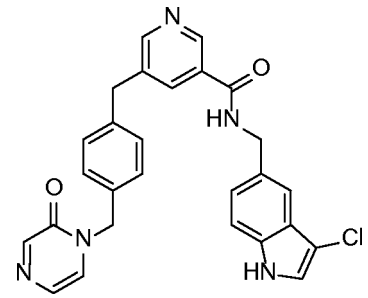


A mixture of 5-(2-(((*tert*-butoxycarbonyl)amino)methyl)benzyl)nicotinic acid (250 mg, crude, 0.42 mmol, 1.0 eq), (3-chloro-1H-indol-5-yl)methanamine HCl salt (100 mg, 0.46 mmol, 1.1 eq), HATU (239 mg, 0.63 mmol,1.5 eq) and DIEA (162 mg, 1.26 mmol, 3.0 eq) in DMF (10 mL) was stirred at rt overnight. The mixture was purified directly by flash chromatography to afford *tert*-butyl 2-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)benzylcarbamate as a yellow solid (132 mg, 62%).

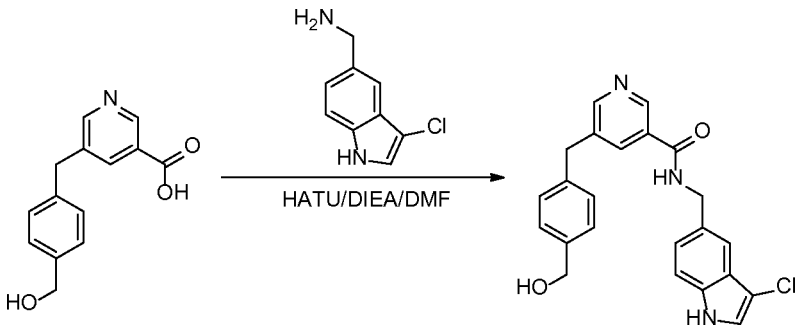


A mixture of *tert*-butyl 2-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)benzylcarbamate (132 mg, 0.26 mmol, 1.0 eq) in HCl/MeOH (25% w/w, 10 mL) was stirred at rt for 2 h. The mixture was purified directly by flash chromatography to afford 5-(2-(aminomethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide as a yellow solid (27 mg, 26%). LRMS ($M+H^+$) m/z calculated 405.15, found 405.1. ^1H NMR (DMSO-d6, 300 MHz) δ 11.37 (s, 1 H), 9.29 (t, 1 H), 8.94 (s, 1 H), 8.58 (s, 1 H), 8.34 (brs, 3 H), 8.00 (s, 1 H), 7.51-7.33 (m, 5 H), 7.21-7.16 (m, 2 H), 4.56 (d, 2 H), 4.19 (s, 2 H), 4.05-4.00 (m, 2 H).

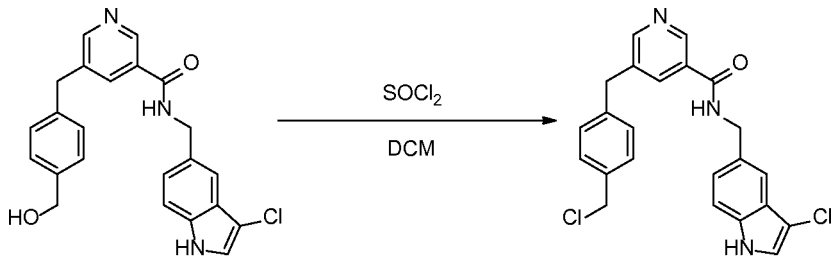
Example 103: Preparation of N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide



N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide

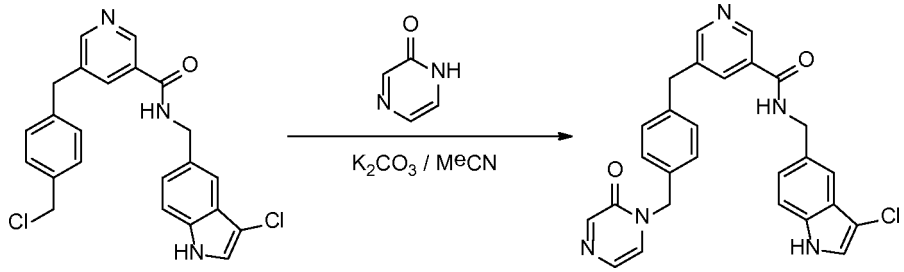


A mixture of 5-(4-(hydroxymethyl)benzyl)nicotinic acid (500 mg, 2.0 mmol, 1.0 eq), (3-chloro-1H-indol-5-yl)methanamine HCl salt (446 mg, 2.0 mmol, 1.0 eq), HATU (782 mg, 2.0 mmol, 1.0 eq) and DIEA (2.0 mL) in DMF (6 mL) was stirred at rt for 2 h and then purified by flash chromatography ($MeCN/H_2O$ = 1/4 to 4/1) to afford N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-(hydroxymethyl)benzyl)nicotinamide as white solid (389 mg, 46%).



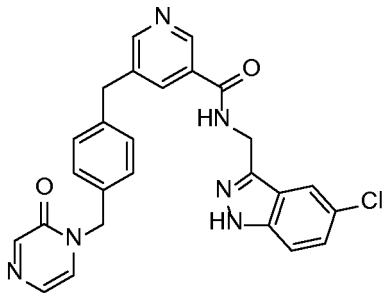
To a solution of N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-(hydroxymethyl)benzyl)nicotinamide (380 mg, 0.93 mmol, 1.0 eq) in 15 ml of DCM was added dropwise $SOCl_2$ (1 mL) in ice-water bath. The mixture was then stirred at rt for 1 h and evaporated under reduced pressure to give an oil, which was purified by flash

chromatography (MeCN/H_2O = 1/2 to 19/1) to afford N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-(chloromethyl)benzyl)nicotinamide (90 mg, 22%).

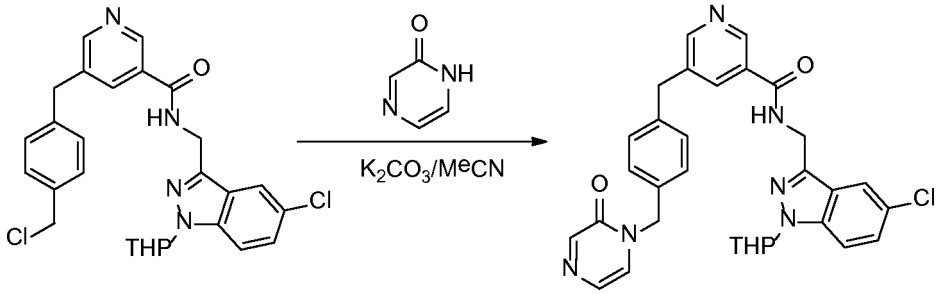


A solution of N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-(chloromethyl)benzyl)nicotinamide (90 mg, 0.21 mmol, 1.0 eq), pyrazin-2(1H)-one (41 mg, 0.42 mmol, 2.0 eq) and K_2CO_3 (58 mg, 0.42 mmol, 2.0 eq) in MeCN (10 mL) was stirred at 80 °C for 2 h and allowed to cool. The mixture was concentrated. The residue was purified by flash chromatography (MeCN/H_2O = 1/2 to 19/1) to afford N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (6.3 mg, 6%). LRMS ($M+H^+$) m/z calculated 484.1, found 484.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.72 (s, 1 H), 8.44 (s, 1 H), 7.97 (s, 1 H), 7.95 (d, 1 H), 7.47 (d, 1 H), 7.40 (s, 1 H), 7.26-7.20 (m, 4 H), 7.16-7.10 (m, 3 H), 7.10-7.08 (m, 1 H), 5.00 (s, 2 H), 4.55 (s, 2 H), 3.96 (s, 2 H).

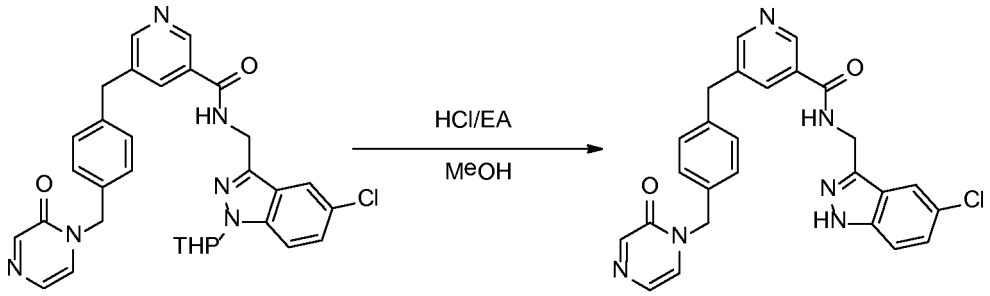
Example 104: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide



N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(4-((2-oxopyrazin-1(2*H*)-yl)methyl)benzyl)nicotinamide

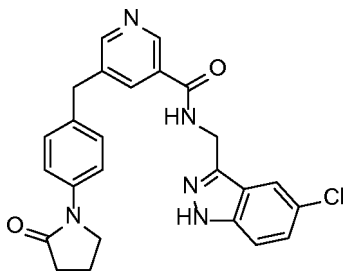


A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(chloromethyl)benzyl)nicotinamide (50 mg, 0.098 mmol, 1.0 eq), pyrazin-2(1H)-one (11 mg, 0.11 mmol, 1.2 eq), and K_2CO_3 (27 mg, 0.19 mmol, 2.0 eq) in MeCN (2 mL) was heated at reflux for 18 h. The resulting suspension was concentrated in vacuo. The residue was purified by flash chromatography (MeCN/H_2O = 1/2 to 19/1) to give N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (37 mg, 66%).

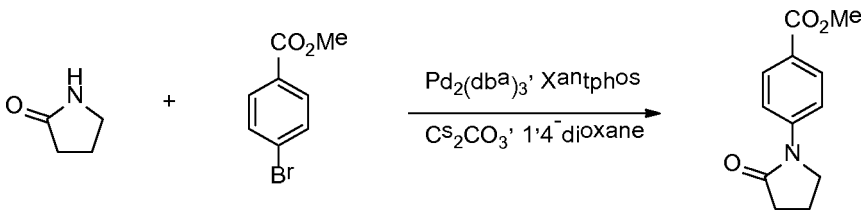


A solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide (37 mg, 0.065 mmol, 1.0 eq) in MeOH (2 mL) and HCl/EA (3 N, 3 mL) was stirred at 40 °C for 3 h. Then the mixture was concentrated. The residue was purified by flash chromatography (MeCN/H_2O = 1/9 to 2/1) to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide as a white solid (19 mg, 60%). LRMS ($M+H^+$) m/z calculated 485.1, found 485.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.07 (s, 1 H), 9.28 (t, 1 H), 8.86 (d, 1 H), 8.62 (d, 1 H), 8.04 (s, 1 H), 8.01 (s, 1 H), 7.89 (d, 1 H), 7.73 (d, 1 H) , 7.52 (d, 1 H), 7.34-7.27 (m, 2 H), 7.25 (m, 4 H), 5.02 (s, 2 H), 4.77 (d, 2 H), 3.99 (s, 2 H).

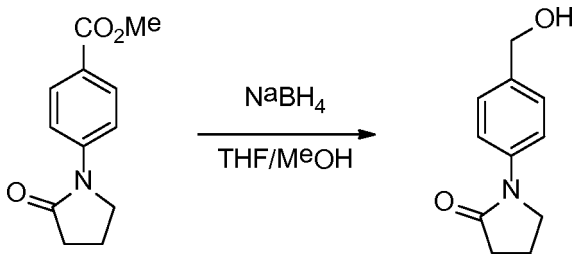
Example 105: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxopyrrolidin-1-yl)benzyl)nicotinamide



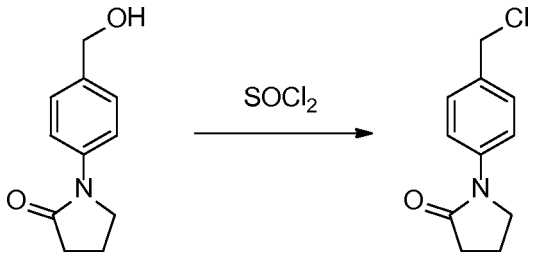
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxopyrrolidin-1-yl)benzyl)nicotinamide



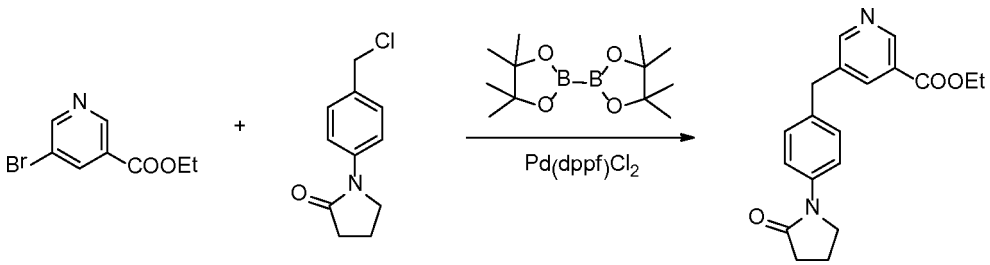
The mixture of pyrrolidin-2-one (3.0 g, 35.3 mmol, 1.0 eq), methyl 4-bromobenzoate (8.8 g, 40.9 mmol, 1.16 eq), tris(dibenzylideneacetone)dipalladium(0) (807 mg, 0.88 mmol, 2.5%), Xantphos (1.53 g, 2.65 mmol, 7.5%) and cesium carbonate (1.60 g, 49.4 mmol, 1.4 eq) in 1,4-dioxane (120 mL) was degassed and refluxed under nitrogen overnight. Then it was concentrated, and the residue was portioned between water and DCM. The DCM layer was separated and washed with water, brine, dried over sodium sulfate, and purified silica gel column (PE/EA = 1/1) to afford methyl 4-(2-oxopyrrolidin-1-yl)benzoate as a white solid (7.0 g, 90%).



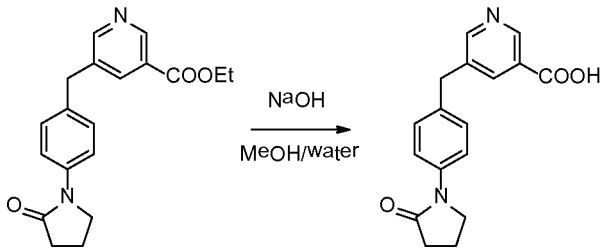
The mixture of methyl 4-(2-oxopyrrolidin-1-yl)benzoate (7.5 g, 34.2 mmol, 1.0 eq), sodium borohydride (7.8 g, 205.6 mmol, 6.0 eq) in THF (200 mL) was heated to reflux, then MeOH was added drop wise carefully until the reaction was complete. After cooling, the mixture was filtered through celite, concentrated, and the residue was dissolved in DCM (100 mL), washed with brine, dried over $MgSO_4$, abd purified silica gel column (PE/EA = 1/2) to afford 1-(4-(hydroxymethyl)phenyl)pyrrolidin-2-one as a white solid (1.68 g, 25%). LRMS ($M+H^+$) m/z calculated 444.2, found 444.2.



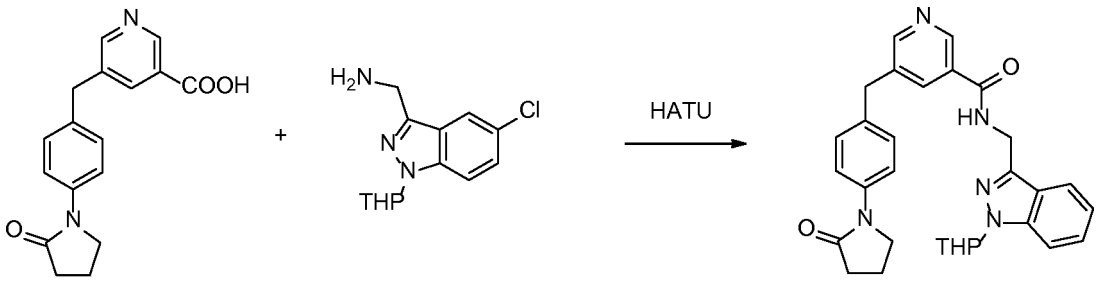
To a solution of 1-(4-(hydroxymethyl)phenyl)pyrrolidin-2-one (208 mg, 1.1 mmol, 1.0 eq) in dry DCM (10 mL) was added thionyl chloride (0.16 mL, 2.2 mmol, 2.0 eq). The reaction mixture was stirred for 30 min, concentrated, and the residue was purified via flash chromatography (PE/DCM/EA = 1/1/1) to afford 1-(4-(chloromethyl)phenyl)pyrrolidin-2-one as a white solid (210 mg, 92%). LRMS ($M+H^+$) m/z calculated 444.2, found 444.2.



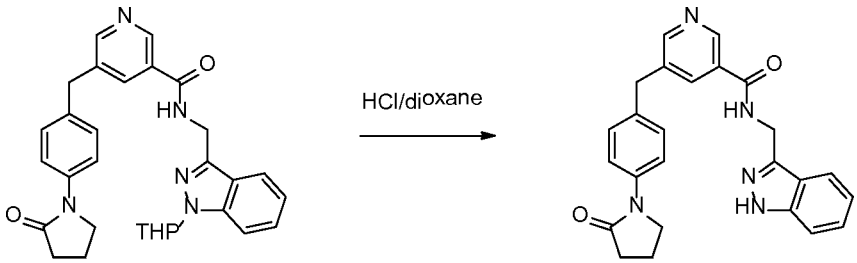
The mixture of ethyl 5-bromonicotinate (345 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (381 mg, 1.5 mmol, 1.5 eq), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (55 mg, 5%) and potassium acetate (441 mg, 4.5 mmol, 4.5 eq) in dioxane (10 mL) was degassed with N_2 and stirred at 80 °C for 3.5 h, then cooled, 1-(4-(chloromethyl)phenyl)pyrrolidin-2-one (210 mg, 1.0 mmol, 1.0 eq), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (55 mg, 5%) and an aqueous solution of sodium carbonate (447 mg, 4.5 mmol, 4.5 eq) in 5 mL of water were added. The mixture was degassed and stirred at 95 °C under N_2 overnight. The reaction mixture was cooled and filtered through celite, concentrated, and the residue was dissolved in DCM (150 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via flash chromatography (5% MeOH in DCM) to afford ethyl 5-(4-(2-oxopyrrolidin-1-yl)benzyl)nicotinate as a yellow solid (170 mg, 52%).



The mixture of ethyl 5-(4-(2-oxopyrrolidin-1-yl)benzyl)nicotinate (170 mg, 0.52 mmol, 1.0 eq) and sodium hydroxide (42 mg, 1.04 mmol, 2.0 eq) in MeOH (3 mL) and water (3 mL) was stirred at rt for 1.5 h, then concentrated. The residue was diluted with water (2 mL) and washed with EA once, then acidified with concentrated HCl till pH 2. The organic phase was concentrated in vacuo to afford 5-(4-(2-oxopyrrolidin-1-yl)benzyl)nicotinic acid as crude which was used without further purification.

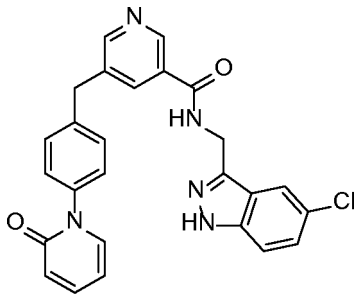


The mixture of 5-(4-(2-oxopyrrolidin-1-yl)benzyl)nicotinic acid (abtanied above), HATU (300 mg, 0.78 mmol, 1.5 eq) and Et_3N (0.3 mL) in DCM (5 mL) was stirred for 15 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (138 mg, 0.52 mmol, 1.0 eq) was added. The reaction mixture was stirred for 1 h, quenched with water, and the DCM layer was washed with brine, dried over $MgSO_4$, purified via silica flash chromatography (5% MeOH in DCM) to afford 5-(4-(2-oxopyrrolidin-1-yl)benzyl)-N-((1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide as a white solid (200 mg, 70%).

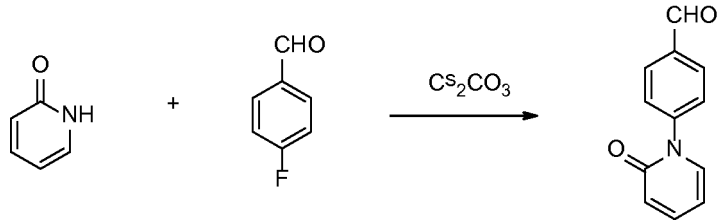


The mixture of 5-(4-(2-oxopyrrolidin-1-yl)benzyl)-N-((1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide (200 mg, 0.36 mmol, 1.0 eq) in MeOH (3 mL) was treated with 5 NHCl/dioxane and stirred for 1 h. then it was concentrated and purified via reverse flash chromatography to afford N-((1H-indazol-3-yl)methyl)-5-(4-(2-oxopyrrolidin-1-yl)benzyl)nicotinamide as a white solid (140 mg, 82%). LRMS ($M+H^+$) m/z calculated 460.1, found 460.1. ^1H NMR ($CDCl_3$ + CD_3OD, 400 MHz) δ 8.83 (s, 1 H), 8.52 (s, 1 H), 8.02 (s, 1 H), 7.84 (s, 1 H), 7.50 (d, 2 H), 7.40 (d, 1 H) , 7.33 (d, 1 H) , 7.19 (d, 2 H) , 4.91 (d, 2 H), 4.02 (s, 2 H), 3.86 (t, 2 H), 2.61 (t, 2 H), 2.19-2.15 (m, 3 H).

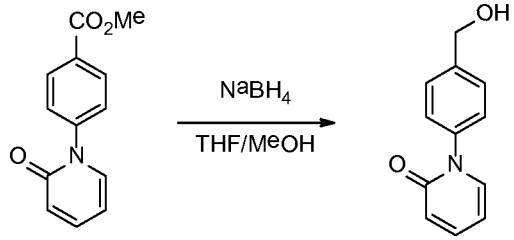
Example 106: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinamide



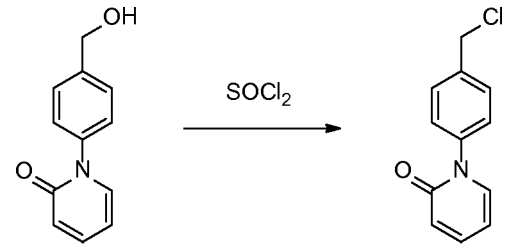
N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(4-(2-oxopyridin-1(2*H*)-yl)benzyl)nicotinamide



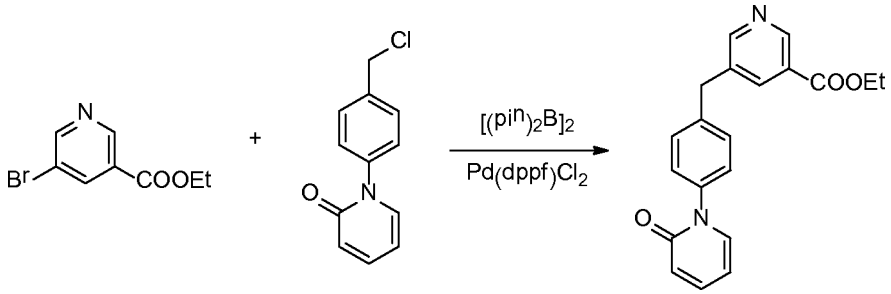
The mixture of pyridin-2(1H)-one (0.95 g, 10.0 mmol, 1.0 eq), 4-fluorobenzaldehyde (1.24 g, 10.0 mmol, 1.0 eq) and Cs_2CO_3 (4.2 g, 13.0 mmol, 1.3 eq) in DMF (50 mL) was stirred at 120 °C overnight. Then it was cooled, poured into water, extracted with EA (50 mLX2), washed with water, brine and purified by reverse flash chromatography to afford 4-(2-oxopyridin-1(2H)-yl)benzaldehyde as a white solid (600 mg).



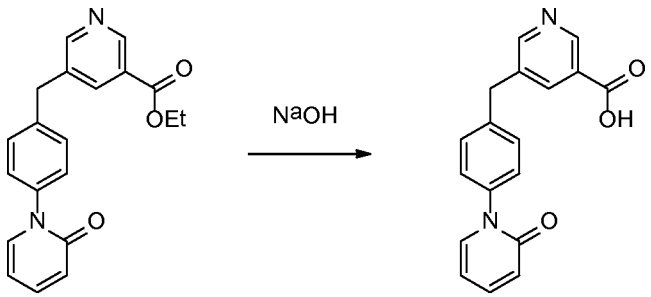
The mixture of 4-(2-oxopyridin-1(2H)-yl)benzaldehyde (300 mg, 1.5 mmol, 1.0 eq), $NaBH_4$ (114 mg, 3.0 mmol, 2.0 eq) in MeOH (7 mL) was stirred at rt overnight. Then it was concentrated, and the residue was purified via silica flash chromatography to afford 1-(4-(hydroxymethyl)phenyl)pyridin-2(1H)-one as a white solid (270 mg, 89%).



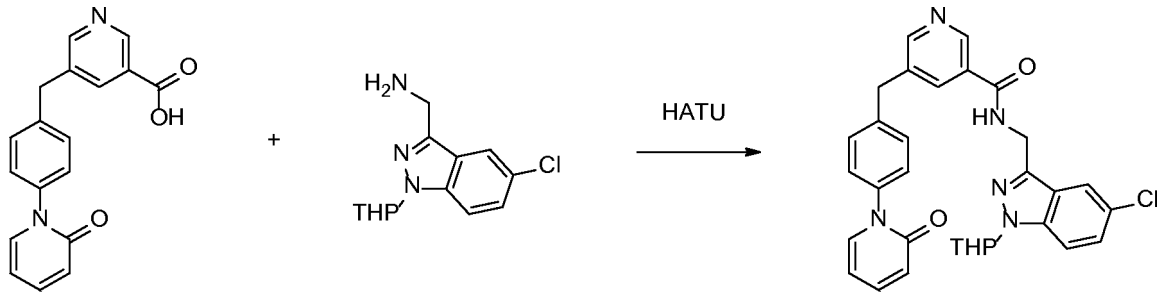
The solution of 1-(4-(hydroxymethyl)phenyl)pyridin-2(1H)-one (270 mg, 1.34 mmol, 1.0 eq) in dry DCM (10 mL) was added $SOCl_2$ (0.19 mL, 2.68 mmol, 2.0 eq). The reaction mixture was stirred for 60 min, and concentrated. The residue was purified silica flash chromatography (EA) to afford 1-(4-(chloromethyl)phenyl)pyridin-2(1H)-one as a white solid (290 mg, quantitative).



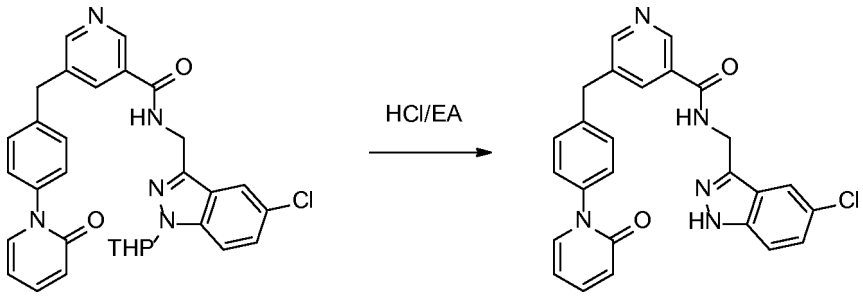
The mixture of ethyl 5-bromonicotinate (345 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (381 mg, 1.5 mmol, 1.5 eq), $Pd(dppf)Cl_2$ (55 mg, 5%) and KOAc (441 mg, 4.5 mmol, 4.5 eq) in dioxane (10 mL) was degassed with N_2 and stirred at 80 °C for 3.5 h. after cooling, 1-(4-(chloromethyl)phenyl)pyridin-2(1H)-one (210 mg, 1.0 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (55 mg, 5%) and an aqueous solution of Na_2CO_3 (447 mg, 4.5 mmol, 4.5 eq) in 5 mL of water were added to this mixture. The mixture was degassed and stirred at 95 °C under N_2 overnight. It was cooled and filtered through celite, concentrated. And the residue was dissolved in DCM (150 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via silica flash chromatography (DCM/MeOH = 20/1) to afford ethyl 5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinate as a yellow solid (170 mg, 52%).



The solution of ethyl 5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinate (300 mg, 0.898 mmol, 1.0 eq) in MeOH (4 mL) was treated with an aqueous solution of NaOH (72 mg, 1.796 mmol, 2.0 eq) in 3 mL of water. The mixture was stirred for 1 h and concentrated. The residue was acidified with 2 N HCl till pH 1 to afford 5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinic acid (220 mg, 81%).

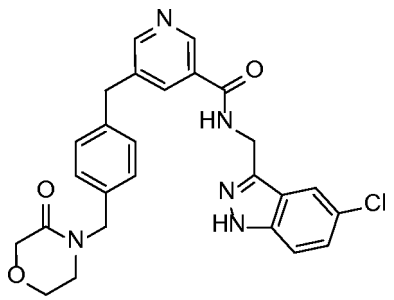


The mixture of 5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinic acid (80 mg, 0.26 mmol, 1.0 eq) and HATU (148 mg, 0.39 mmol, 1.5 eq) in DMF (3 mL) and DIPEA (0.3 ml) was stirred for 30 min, and then (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (69 mg, 0.26 mmol, 1.0 eq) was added. The reaction was stirred at rt for 1 h, quenched with water, and extracted with DCM. The DCM layer was washed with brine, and purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinamide as a white solid (100 mg, 69%).

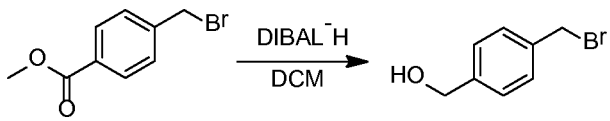


The solutuion of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinamide (100 mg, 0.18 mmol, 1.0 eq) in MeOH (3 mL) was treated with 2 N HCl/EA and stirred for 30 min. After concentration, the residue was purified by flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinamide as a white solid (40 mg, 47%). LRMS ($M+H^+$) m/z calculated 470.1, found 470.1. ^1H NMR (DMSO-d6, 400 MHz) δ 13.10 (s, 1 H), 9.34 (s, 1 H), 8.89 (s, 1 H), 8.70 (s, 1 H), 8.15 (s, 1 H), 7.92 (s, 1 H), 7.74-7.15 (m, 8 H), 6.56- 6.38 (m, 1 H), 6.28 (s, 1 H), 4.80 (s, 2 H), 4.10 (s, 3 H).

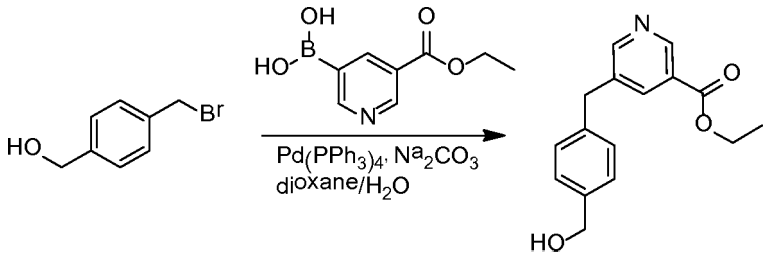
Example 107: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((3-oxomorpholino)methyl)benzyl)nicotinamide



N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(4-((3-oxomorpholino)methyl)benzyl)nicotinamide

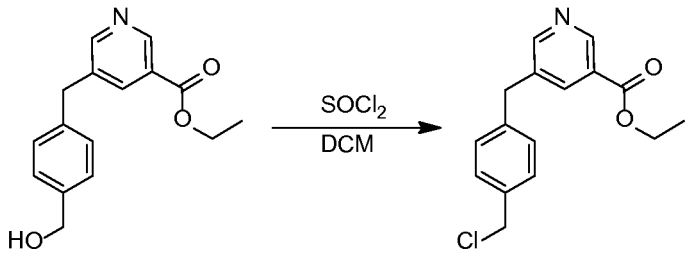


To a solution of methyl 4-(bromomethyl)benzoate (2.3 g, 0.01 mol) in dry DCM (80 mL) was added DIBAL-H (22 mL, 0.03 mol) at -78 °C under N_2. The mixture was stirred at -78 °C for 1.5 h. The reaction mixture was quenched by careful addition of H_2O (50 mL), and then extracted with DCM (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford (4-(bromomethyl)phenyl)methanol as a white solid (1.6 g, 80%).

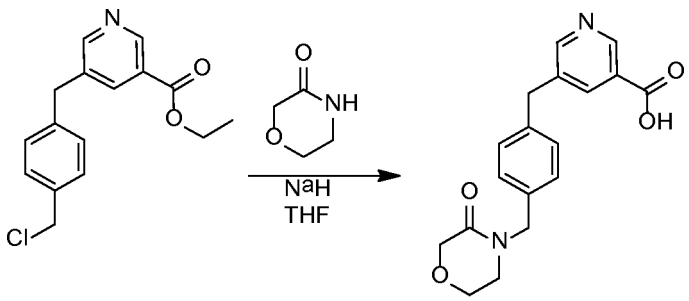


A mixture of (4-(bromomethyl)phenyl)methanol (200 mg, 1.0 mmol), (5-(ethoxycarbonyl)pyridin-3-yl)boronic acid (195 mg, 1.0 mmol), $Pd(PPh_4)_3$ (116 mg, 0.1 mmol), and Na_2CO_3 (318 mg, 3.0 mmol) in 1,4-

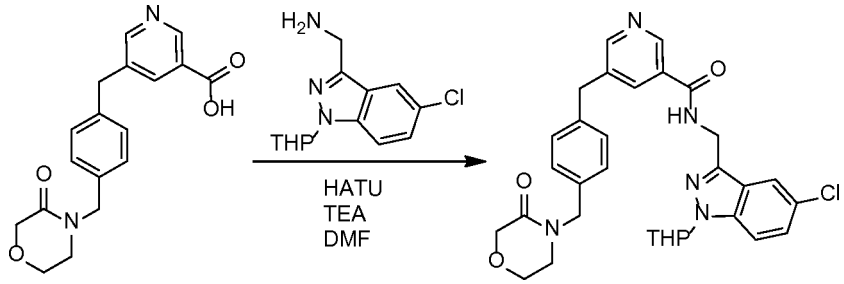
dioxane (10 mL) and H_2O (2 mL) was heated at 85 °C overnight under N_2. The mixture was diluted with water (100 mL) and extracted with EA (50 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified via prep-HPLC to afforded ethyl 5-(4-(hydroxymethyl)benzyl)nicotinate as a white solid (100 mg, 37%).



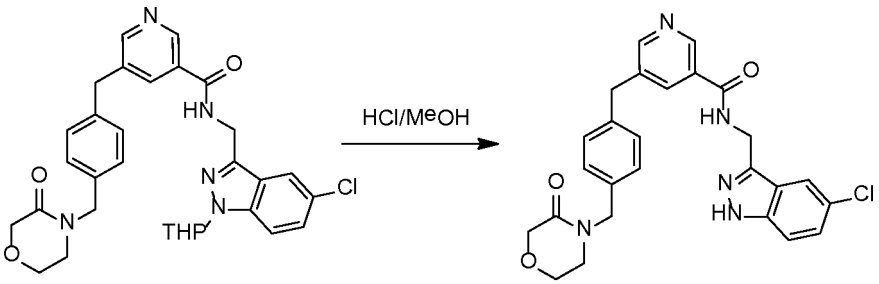
A mixture of ethyl 5-(4-(hydroxymethyl)benzyl)nicotinate (100 mg, 0.36 mmol), and $SOCl_2$ (0.04 mL, 0.36 mmol) in DCM (5 mL) was stirred at rt for 30 min. The mixture was concentrated to afford ethyl 5-(4-(chloromethyl)benzyl)nicotinate as a white solid (100 mg, 65%).



To a suspension of NaH (20.8 mg, 0.52 mmol) in dry DMF (2 mL) was added morpholin-3-one (52 mg, 0.52 mmol) at rt. The mixture was stirred at rt for 30 min, then ethyl 5-(4-(chloromethyl)benzyl)nicotinate (100 mg, 0.34 mmol) in 2 mL of DMF was added. The mixture was stirred at rt for 2 h, and then concentrated to afford 5-(4-((3-oxomorpholino)methyl)benzyl)nicotinic acid as a colorless oil (100 mg, 92%).

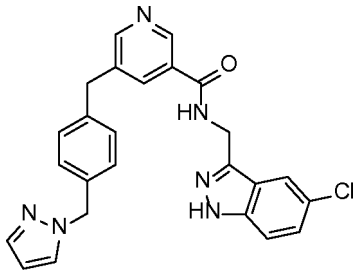


A mixture of 5-(4-((3-oxomorpholino)methyl)benzyl)nicotinic acid (56 mg, 0.17 mmol), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (53 mg, 0.18 mmol), HATU (98 mg, 0.28 mmol) and TEA (0.07 mL, 0.51 mmol) in DMF (5 mL) was stirred at rt for 2 h. The mixture was concentrated and purified via prep-HPLC to afforded N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((3-oxomorpholino)methyl)benzyl)nicotinamide as a white solid (30 mg, 30%).

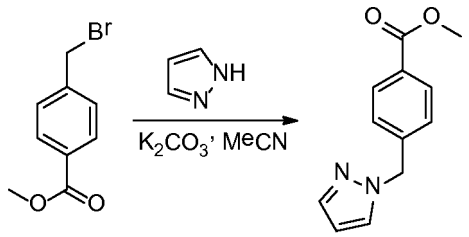


A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((3-oxomorpholino)methyl)benzyl)nicotinamide (20 mg, 0.03 mmol) in HCl/MeOH (5 mL) was stirred at rt for overnight. The mixture was concentrated and purified by prep-HPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((3-oxomorpholino)methyl)benzyl)nicotinamide as a white solid (6 mg, 30%). LRMS ($M+H^+$) m/z calculated 490, found 490.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.18 (s, 1 H), 8.92 (d, 2 H), 7.92 (s, 1 H), 7.52-7.50 (d, 1 H), 7.44-7.42 (d, 1 H), 7.33-7.32 (m, 4 H), 4.97 (s, 2 H), 4.62 (s, 2 H), 4.31 (s, 2 H), 4.20 (s, 2 H), 3.87-3.85 (m, 2 H).

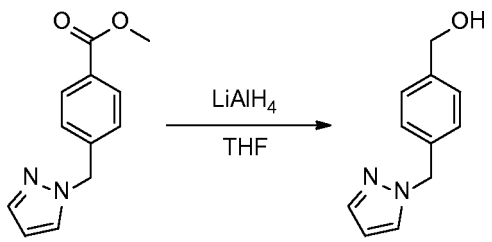
Example 108: Preparation of 5-(4-((1H-pyrazol-1-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide



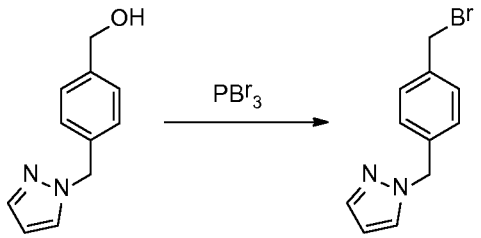
5-(4-((1*H*-pyrazol-1-yl)methyl)benzyl)-*N*-((5-chloro-1*H*-indazol-3-yl)methyl)nicotinamide



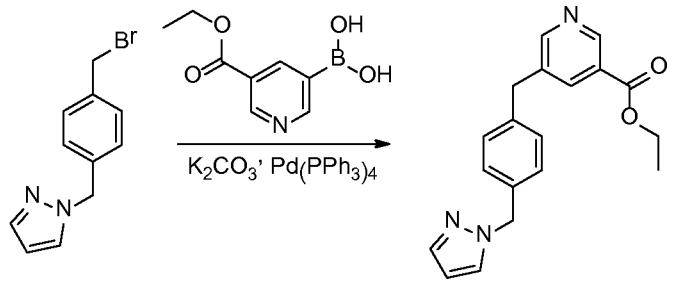
To a solution of methyl 4-(bromomethyl)benzoate (5.0 g, 21.8 mmol, 1.0 eq) in MeCN (5 mL), 1H-pyrazole (2.2 g, 32.7 mmol, 1.5 eq) and K_2CO_3 (6.0 g, 43.7 mmol, 2.0 eq) were added and the mixture was stirred at 70 °C for 5 h. The mixture was concentrated, poured into water, extracted with EA (3x100 mL). The combined organic layers were washed with brine, concentrated, purified by column chromatography (PE/EA = 5:1) to afford methyl 4-((1H-pyrazol-1-yl)methyl)benzoate as a white solid (3.0 g, 63.8%).



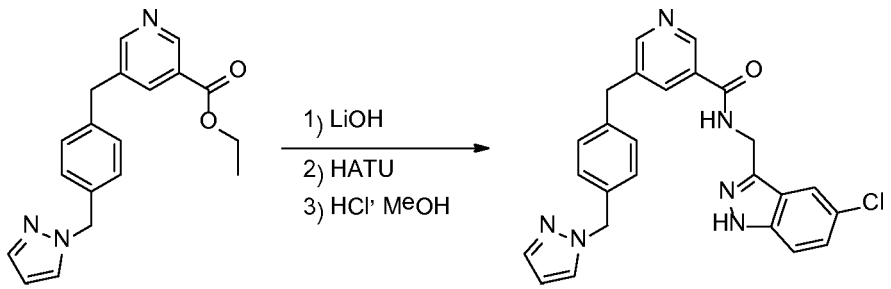
To a solution of methyl 4-((1H-pyrazol-1-yl)methyl)benzoate (800 mg, 3.70 mmol, 1.0 eq) in THF (10 mL) was added $LiAlH_4$ (281 mg, 7.4 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction was quenched with Na_2SO_4-$10H_2O$, poured into water, extracted with EA (3 x50 mL). The combined organic layers were washed with brine, and concentrated to afford (4-((1H-pyrazol-1-yl)methyl)phenyl)methanol as a yellow oil (600 mg, 86%).



To a solution of (4-((1H-pyrazol-1-yl)methyl)phenyl)methanol (600 mg, 3.19 mmol, 1.0 eq) in THF (10 mL) was added PBr_3 (2.6 g, 9.56 mmol) at 0 °C and the mixture was stirred at that temperature for 2 h. The mixture was poured into ice-water, extracted with DCM (3x50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated to afford 1-(4-(bromomethyl)benzyl)-1H-pyrazole as a white solid (600 mg, 75%).

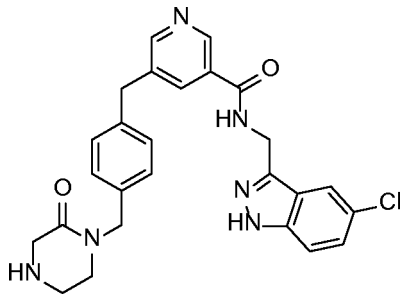


A mixture of (5-(ethoxycarbonyl)pyridin-3-yl)boronic acid (233 mg, 1.19 mmol, 1.0 eq) and 1-(4-(bromomethyl)benzyl)-1H-pyrazole (300 mg, 1.19 mmol, 1.0 eq), $Pd(PPh_3)_4$ (140 mg, 0.12 mmol, 0.1 eq) and Na_2CO_3 (140 mg, 3.57 mmol, 3.0 eq) in dioxane/H_2O (7 mL / 1 mL) was stirred at 100 °C under N_2 atmosphere overnight. Then the mixture was filtered and the filtrate concentrated. The residue was poured into water, extracted with EA (3x20 mL). The combined organic layers were washed with brine, and concentrated. The residue was purified by prep-TLC to afford ethyl 5-(4-((1H-pyrazol-1-yl)methyl)benzyl)nicotinate as a brown oil (100 mg, 26%).

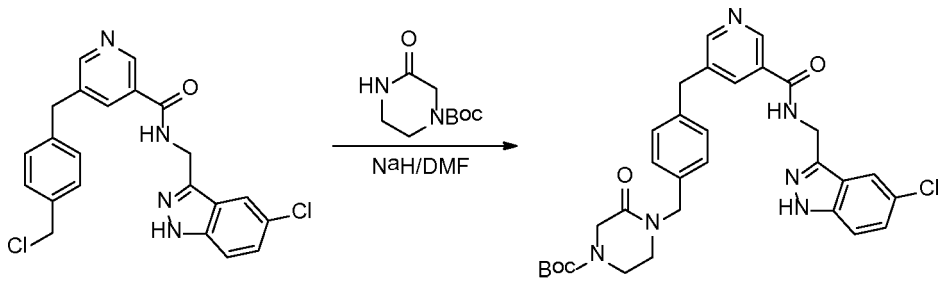


5-(4-((1H-Pyrazol-1-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide (8 mg, HCl salt) was prepared from 5-(4-((1H-pyrazol-1-yl)methyl)benzyl)nicotinate as described for N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2-chlorobenzyl)nicotinamide. LRMS ($M+H^+$) m/z caculated 456.15, found 456.2. ^1H NMR (CD_3OD, 400 MHz) δ 9.06 (s, 1 H), 8.79 (d, 2 H), 7.99 (s, 1 H), 7.83(d, 2 H), 7.41 (d, 1 H), 7.28-7.18 (m, 5 H), 6.50 (s, 1 H), 5.41 (s, 2 H), 4.84 (s, 2 H), 4.20 (s, 2 H).

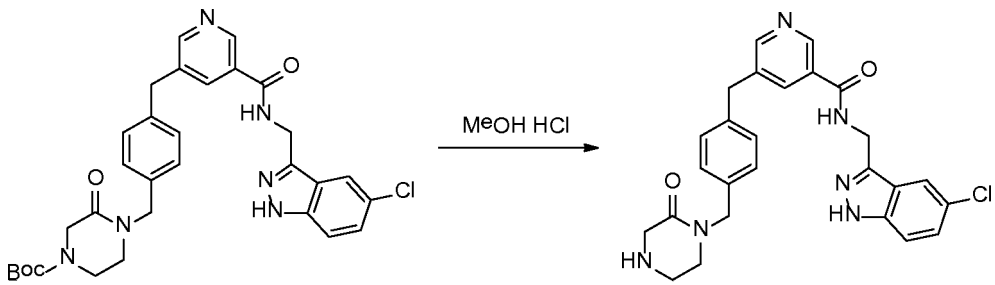
Example 109: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopiperazin-1-yl)methyl)benzyl)nicotinamide



N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(4-((2-oxopiperazin-1-yl)methyl)benzyl)nicotinamide

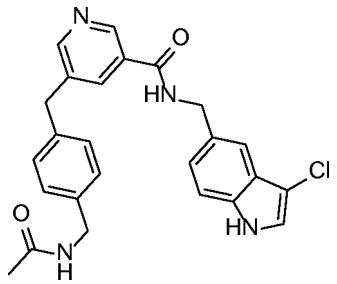


To a solution of NaH (40 mg, 0.99 mmol) in DMF (3 mL) was added *tert*-butyl 3-oxopiperazine-1-carboxylate (330 mg, 1.65 mmol). The mixture was stirred at rt for 0.5 h, N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(chloromethyl)benzyl)nicotinamide (70 mg, 0.16 mmol, 1.0 eq) was then added. The mixture was stirred at rt for 1 h. Water (0.5 mL) was added into the reaction mixture to quench the reaction. The mixture was evaporated to dryness, and the residue was purified by prep-HPLC to afford *tert*-butyl 4-(4-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)benzyl)-3-oxopiperazine-1-carboxylate as a yellow solid (18 mg, 19%).

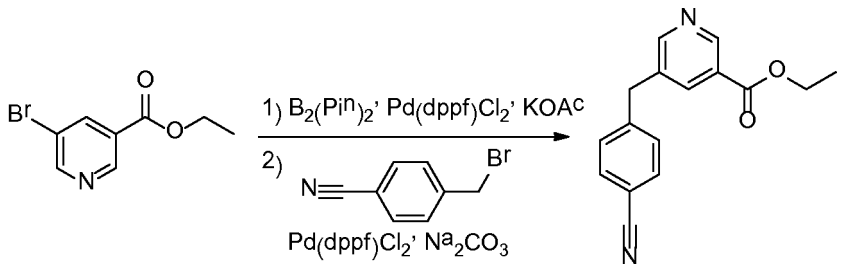


A mixture of *tert*-butyl 4-(4-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)benzyl)-3-oxopiperazine-1-carboxylate (18 mg, 0.036 mmol, 1.0 eq) in HCl/MeOH (25% w/w, 4 mL) was stirred at rt for 4 h. The mixture was purified directly by flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopiperazin-1-yl)methyl)benzyl)nicotinamide as a yellow solid (10 mg, 67%). LRMS ($M+H^+$) m/z calculated 489.17, found 489.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.05 (s, 1 H), 8.78 (d, 2 H), 7.80 (s, 1 H), 7.40 (d, 1 H), 7.21-7.26 (m, 5H), 4.83 (s, 2 H), 4.53 (s, 2 H), 4.17 (s, 2 H), 3.82 (s, 2 H), 3.41-3.45 (m, 4 H).

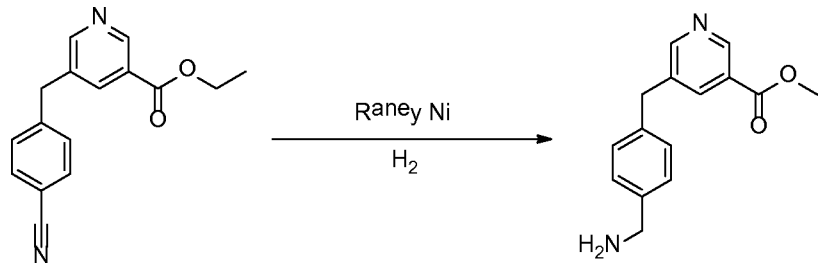
Example 110: Preparation of 5-(4-(acetamidomethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



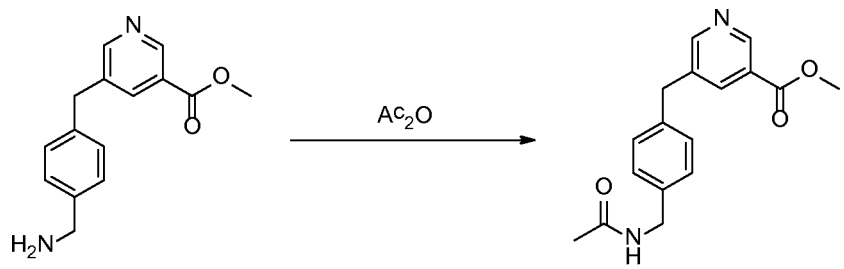
5-(4-(acetamidomethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



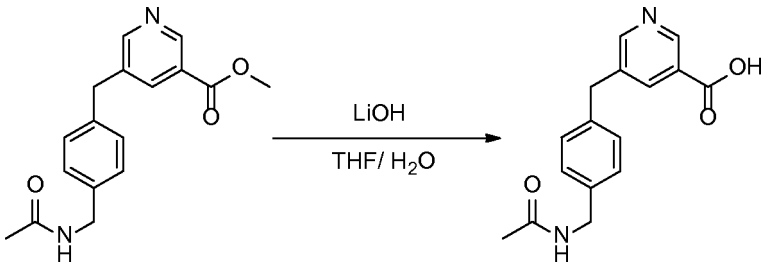
To a solution of ethyl 5-bromonicotinate (5 g, 21.73 mmol, 1 eq) in 1,4-dioxane was added $B_2(Pin)_2$ (6.1 g, 23.91 mmol, 1.1 eq), KOAc (4.3 g, 43.46 mmol, 2 eq), and $Pd(dppf)Cl_2$ (1.59 g, 2.17 mmol, 0.1 eq) under N_2. The mixture was stirred at 90 °C for 3 h. Then to the mixture was added 4-(bromomethyl)benzonitrile (4.3 g, 21.73 mmol, 1 eq), water, and Na_2CO_3 (4.6 g, 43.46 mmol, 2 eq). The mixture was stirred at 90 °C for 3 h, and then poured into water, extracted with EA. The organics was concentrated and purified via flash chromatography (PE/EtOAc = 5/1) to afford ethyl 5-(4-cyanobenzyl)nicotinate as a yellow solid (3.5 g, 60 %).



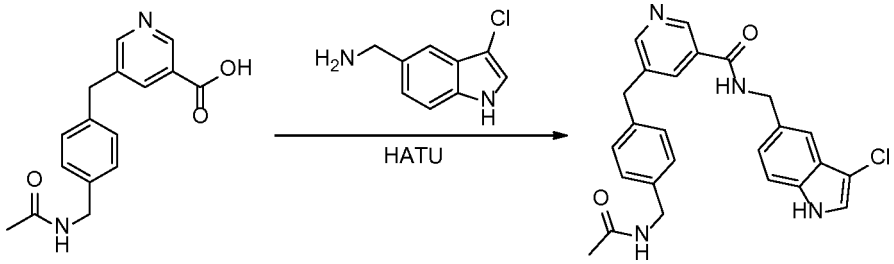
To a solution of ethyl 5-(4-cyanobenzyl)nicotinate (2 g, 7.51 mmol , 1 eq) in MeOH was added Raney Ni. The mixture was stirred at rt overnight under H_2. The mixture was filtered, concentrated, and purified by flsh chromatography (DCM/MeOH = 20/1) to afford methyl 5-(4-(aminomethyl)benzyl)nicotinate as a yellow solid (300 mg, 16 %).



To a solution of methyl 5-(4-(aminomethyl)benzyl)nicotinate (100 mg, 0.39 mmol, 1 eq) in DCM was added Ac_2O (60 mg, 0.59 mmol, 1.5 eq). The mixture was stirred at rt for 2 h, and concentrated. The residue was used for the next step without further purification.

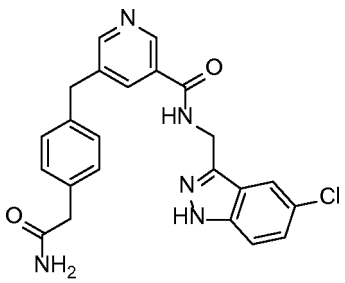


To a solution of methyl 5-(4-(acetamidomethyl)benzyl)nicotinate (100 mg, 0.34 mmol, 1 eq) in THF/H_2O was added LiOH (40 mg, 1.7 mmol, 5 eq), and the mixture was stirred at rt for 2 h. The mixture was acidified to pH 6 with conc. HCl, and concentrated. The residue was used for the next step without purification.

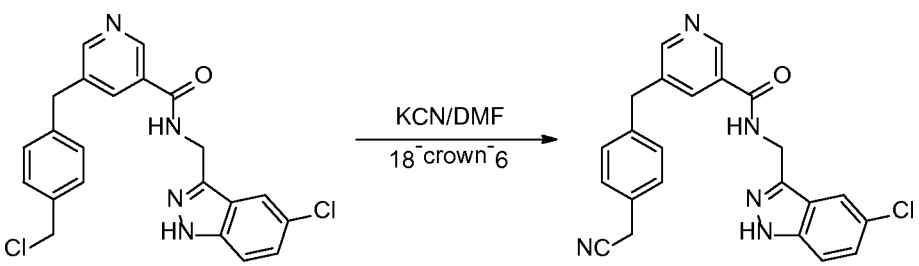


To a solution of 5-(4-(acetamidomethyl)benzyl)nicotinic acid (100 mg, 0.35 mmol, 1 eq) in DMF was added (3-chloro-1H-indol-5-yl)methanamine (63 mg, 0.35 mmol, 1 eq), HATU (160 mg, 0.42 mmol, 1.2 eq), and TEA (71 mg, 0.70 mmol, 2 eq). The mixture was stirred at rt overnight, then poured into water and extracted with EtOAc. The organics was concentrated and purified by prep-HPLC to afford 5-(4-(acetamidomethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide as a white solid (5 mg, 3 %). LCMS ($M+H^+$) m/z calculated 447.2, found 447.2. ^1H NMR (CD_3OD, 400 MHz) δ 10.77-10.76 (m, 1 H) , 9.23-9.20 (m, 1 H), 8.87 (s, 1 H), 8.60-8.56 (m, 1 H), 8.13 (s , 1 H), 7.53 (s, 1 H), 7.39-7.22 (m, 7 H), 4.71-4.68 (m, 1 H), 4.34 (d, 2 H), 4.08 (d, 2 H), 1.99 (s, 3 H).

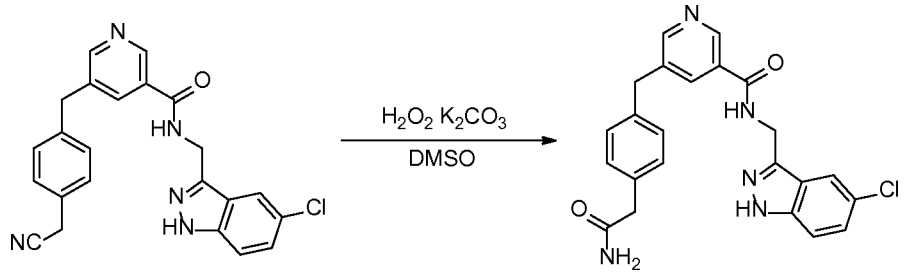
Example 111: Preparation of 5-(4-(2-amino-2-oxoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide



5-(4-(2-amino-2-oxoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide

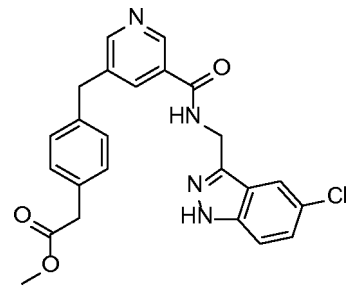


To a solution of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(chloromethyl)benzyl)nicotinamide (120 mg, 0.28 mmol) in DMF (5 mL) were added KCN (18 mg, 0.28 mmol), and 18-crown-6 (7 mg, 0.28mmol). The mixture was stirred at 70 °C for 8 h. The mixture was cooled to rt. Water (20 mL) was added into the reaction mixture, then the mixture was extracted with EA (20 mL x 3). The organic phase was evaporated to dryness, and the residue was purified by flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(cyanomethyl)benzyl)nicotinamide as a yellow solid (60 mg, 50%).

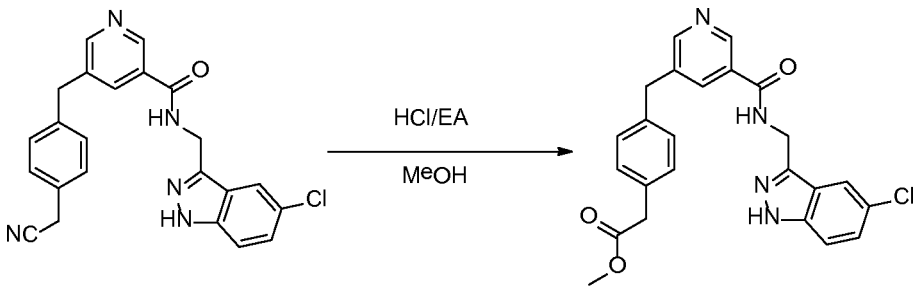


To a solution of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(cyanomethyl)benzyl)nicotinamide (60 mg, 0.14 mmol, 1.0 eq) in DMSO (4 mL) were added 30% H_2O_2 (1.5 mL) and K_2CO_3 (16 mg, 0.11 mmol). The mixture was stirred at 50 °C overnight. The mixture was purified directly by flash chromatography to afford 5-(4-(2-amino-2-oxoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide as a white solid (20 mg, 32%). LRMS ($M+H^+$) m/z calculated 434.13, found 434.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.29 (t, 1 H), 8.86 (s, 1 H), 8.62 (s, 1 H), 8.06 (s, 1 H), 7.91 (s, 1 H), 7.53 (d, 1 H), 7.41 (s, 1 H), 7.32 (m, 1 H), 7.17 (s, 4 H), 6.83 (s, 1 H), 4.78 (d, 2 H), 3.98 (s, 2 H), 3.30 (d, 2 H).

Example 112: Preparation of methyl 2-(4-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)acetate



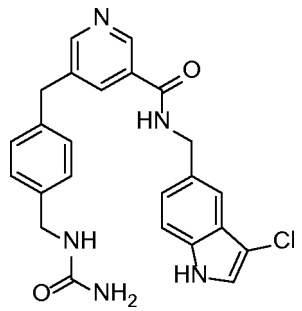
methyl 2-(4-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)acetate



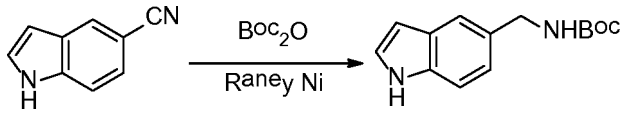
A solution of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(cyanomethyl)benzyl)nicotinamide (30 mg, 0.072 mmol, 1.0 eq) in MeOH (3 mL) and HCl/EA (3 N, 5 mL) was stirred at 50 °C for 20 h. Then the mixture was concentrated in vacuo to give an oil, which was purified by flash chromatography ($MeCN/H_2O$ = 1/2 to 19/1) to afford methyl 2-(4-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)acetate

as a white solid (27 mg, 83%). LRMS ($M+H^+$) m/z calculated 449.1, found 449.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.12 (s, 1 H), 9.40 (t, 1 H), 8.95 (s, 1 H), 8.72 (s, 1 H), 8.24 (s, 1 H), 7.91 (s, 1 H), 7.53 (d, 1 H) , 7.33 (m, 1 H), 7.24-7.17 (m, 4 H), 4.79 (d, 2 H), 4.07 (s, 2 H), 3.62 (s, 2 H), 3.58 (s, 3 H).

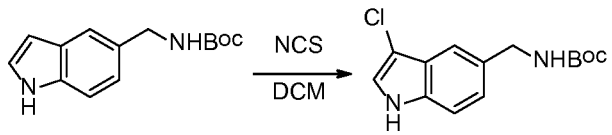
Example 113: Preparation of N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-(ureidomethyl)benzyl)nicotinamide



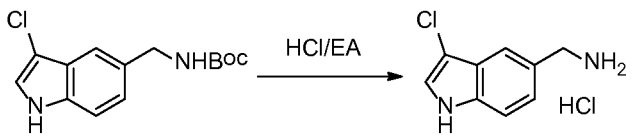
N-((3-chloro-1*H*-indol-5-yl)methyl)-5-(4-(ureidomethyl)benzyl)nicotinamide



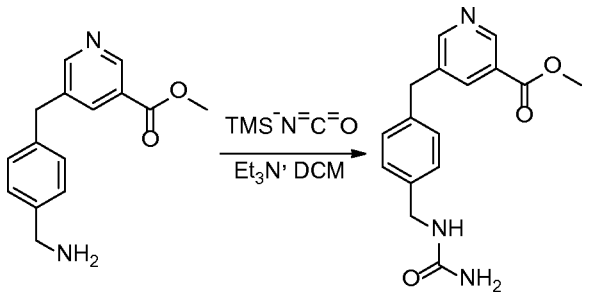
To a solution of 1H-indole-5-carbonitrile (13.9 g, 97.7 mmol, 1.0 eq) in MeOH (280 mL) was added Boc_2O (42.6 g, 196 mmol, 2.0 eq) and Raney Ni (about 1.4 g). The mixture was hydrogenated at rt under 50 Psi overnight. The mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified on silica gel column (PE/EA = 10/1 to 4/1) to afford *tert*-butyl ((1H-indol-5-yl)methyl)carbamate as a yellow oil (13.2 g, 55%).



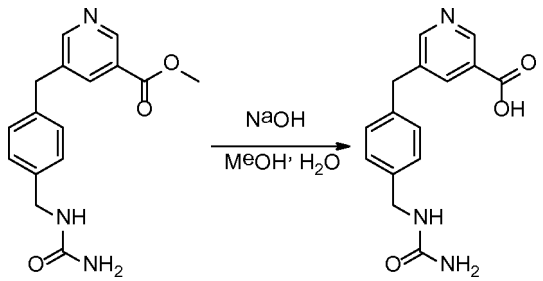
To a solution of *tert*-butyl ((1H-indol-5-yl)methyl)carbamate (13.2 g, 53.6 mmol, 1.0 eq) in DCM (140 mL) was added portions NCS (7.13 g, 53.6 mmol, 1.0 eq) at 0 °C. The mixture was hydrogenated at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was purified on silica gel column (PE/EA = 10/1 to 4/1) to afford *tert*-butyl ((3-chloro-1H-indol-5-yl)methyl)carbamate as a white solid (9.7 g, 65%).



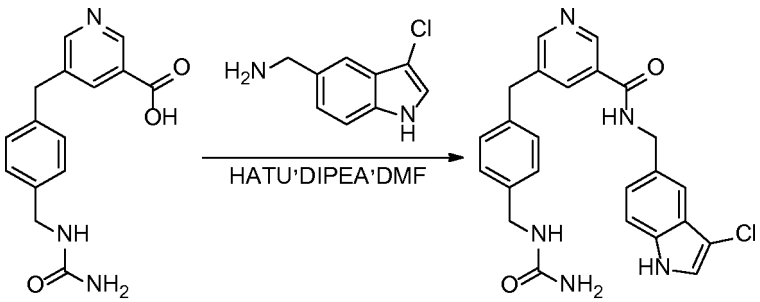
To a solution of *tert*-butyl ((3-chloro-1H-indol-5-yl)methyl)carbamate (9.7 g, 34.6 mmol, 1.0 eq) in EA (40 mL) was added HCl/EA (40 mL, 80 mmol) at 0 °C. The mixture was stirred at rt overnight. The mixture was filtered. The filtered cake was dryness under reduced pressure to afford (3-chloro-1H-indol-5-yl)methanamine HCl salt as a gray solid (6.0 g, 80%).



To a solution of methyl 5-(4-(aminomethyl)benzyl)nicotinate (160 mg, 0.62 mmol, 1.0 eq) in DCM (2 mL) were added Et_3N (250 mg, 2.48 mmol, 4.0 eq) and isocyanatotrimethylsilane (214 mg, 1.86 mmol, 3.0 eq) at 0 °C. The mixture was stirred at rt overnight. The mixture was mixed with saturated $NaHCO_3$ (10 mL). The mixture was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford methyl 5-(4-(ureidomethyl)benzyl)nicotinate as a white solid (70 mg, 38%).

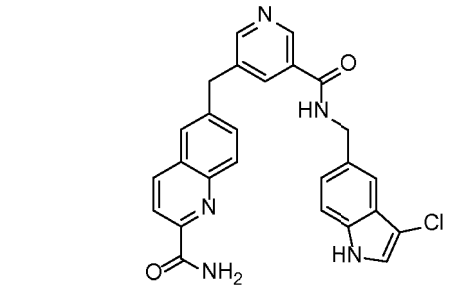


To a solution of methyl 5-(4-(ureidomethyl)benzyl)nicotinate (70 mg, 0.23 mmol, 1.0 eq) in MeOH (1 mL) and H_2O (1 mL) was added NaOH (28 mg, 0.69 mmol, 3.0 eq). The mixture was heated at 60 °C for 2 h. The mixture was concentrated to remove MeOH, then diluted with ice-water (5 mL) and acidified with 1 N HCl to pH 2-3. The mixture was concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (10 mL) and filtered. The filtrate was concentrated under reduced pressure to afford 5-(4-(ureidomethyl)benzyl)nicotinic acid as a yellow solid (200 mg crude, quant).

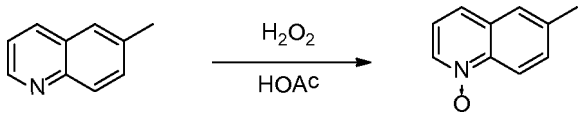


To a solution of 5-(4-(ureidomethyl)benzyl)nicotinic acid (200 mg crude, 0.23 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (89 mg, 0.69 mmol, 3.0 eq) and HATU (105 mg, 0.28 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (3-chloro-1H-indol-5-yl)methanamine (55 mg, 0.25 mmol, 1.1 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was purified via flash chromatography to afford N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-(ureidomethyl)benzyl)nicotinamide as a white solid (6 mg, 6%). LRMS ($M+H^+$) m/z caculated 448.1, found 448.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.34 (brs, 1 H), 9.22 (s, 1 H), 8.89 (s, 1 H), 8.62 (s, 1 H), 8.05 (s, 1 H), 7.50-7.40 (m, 3 H), 7.38-7.15 (m, 5 H), 6.36 (s, 1 H), 5.49 (d, 2 H), 4.57 (d, 2 H), 4.12 (s, 2 H), 4.00 (d, 2 H).

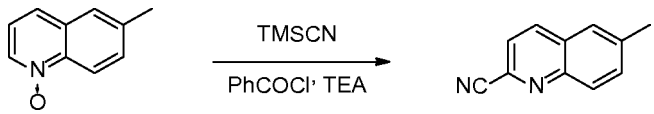
Example 114: Preparation of 6-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)quinoline-2-carboxamide



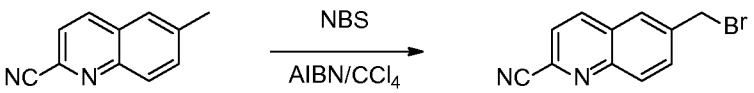
6-((5-(((3-chloro-1*H*-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)quinoline-2-carboxamide



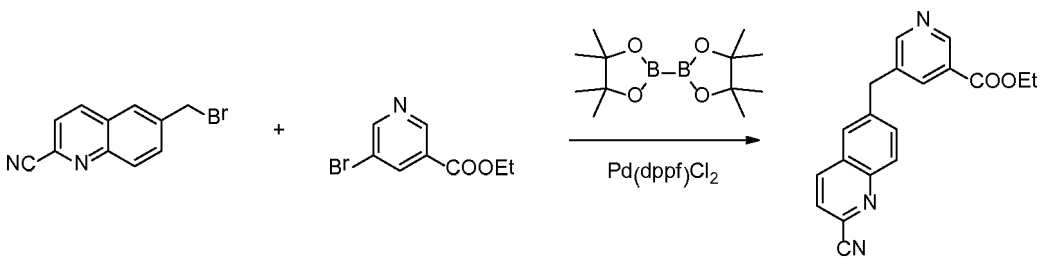
To a solution of 6-methylquinoline (10.0 g, 69.9 mmol, 1.0 eq) in HOAc (150 mL) was added 30% H_2O_2 (100 mL), The reaction mixture was heated to 70 °C and stirred overnight, then cooled, and water (100 mL) was added, then Na_2SO_3 was added portion wise to quench excess H_2O_2 while cooling in ice bath. The reaction mixture was extracted with DCM and the organic phase was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness to afford 6-methylquinoline 1-oxide as a brown oil (7.2 g, 64%).



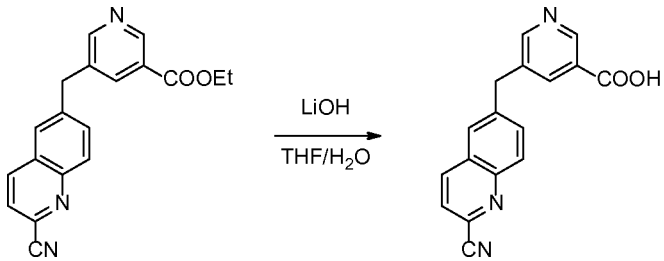
To a solution of 6-methylquinoline 1-oxide (7.2 g, 45.2 mmol, 1.0 eq) in trimethylsilycyanide (17.0 mL, 135.8 mmol, 3.0 eq) was added benzoyl chloride (15.6 mL, 135.8 mmol, 3.0 eq) while cooling in ice-water bath followed by triethylamine (18.9 mL, 135.8 mmol, 3.0 eq). The reaction was stirred for 1 h. The mixture was diluted with DCM, washed once with saturated aqueous $NaHCO_3$ carefully, then washed with water, brine, dried over anhydrous sodium sulfate, and purified on silica gel column (PE/DCM/EA = 10/1/1) and then triturated from EtOH to afford 6-methylquinoline-2-carbonitrile as a yellow solid (6.0 g, 78%).



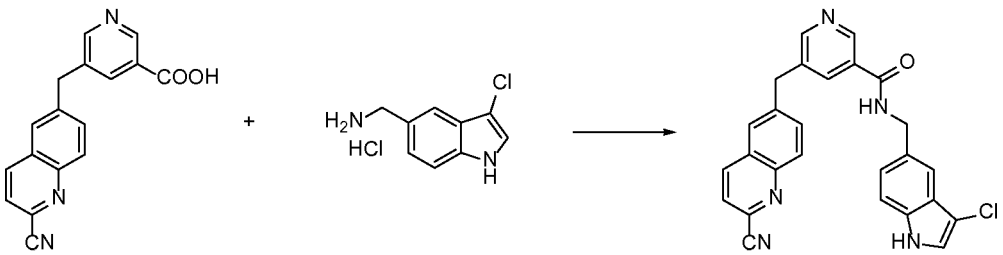
The mixture of 6-methylquinoline-2-carbonitrile (3.7 g, 22.0 mmol, 1.0 eq), NBS (3.9 g, 22.0 mmol, 1.0 eq) and AIBN (72 mg, 2 mol%) in tetrachloride carbon (100 mL) was refluxed for 3 h, then cooled and concentrated to dryness. The residue was triturated from DCM, filtered and dried to afford 6-(bromomethyl)quinoline-2-carbonitrile as a white solid (4.0 g, 74%).



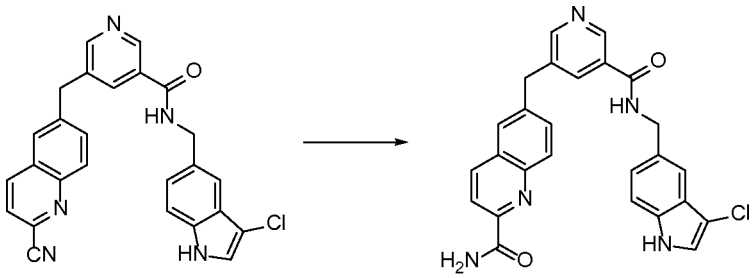
The mixture of ethyl 5-bromonictic acid (1.86 g, 8.1 mmol, 1.0 eq), BPDB (2.06 g, 8.1 mmool, 1.0 eq), potassium acetate (2.38 g, 24.3 mmol, 3.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (296 mg, 5 mol%) were mixed in 1,4-dioxane (100 mL). The mixture was degassed with nitrogen, heated to 85 °C and stirred for 16 h, then cooled to rt, and 6-(bromomethyl)quinoline-2-carbonitrile (2.0 g, 8.1 mmol, 1.0 eq), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (296 mg, 5 mol%) and sodium carbonate (2.57 g, 24.3 mmol, 3.0 eq, dissolved in 30 mL of water) were added. The mixture was degassed, heated to 95 °C and stirred overnight. Cooled and the mixture was filtered through celite, water (100 mL) and DCM (100 mL) were added to the filtrate. The DCM layer was separated and washed with brine, dried over anhydrous sodium sulfate, and purified on silica gel column to afford ethyl 5-((2-cyanoquinolin-6-yl)methyl)nicotinate as a red solid (670 mg, 26%).



To the solution of ethyl 5-((2-cyanoquinolin-6-yl)methyl)nicotinate (670 mg, 2.1 mmol, 1.0 eq) in THF (6 mL) was added an aqueous solution of lithium hydroxide monohydrate (177 mg, 4.2 mmol, 2.0 eq) in water (3 mL). The reaction was stirred for 2 h, then acidified with 2 N HCl to pH 3. DCM (50 mL) and water (50 mL) were added, and the DCM layer was separated and washed with brine, dried over anhydrous sodium sulfate, and purified via flash chromatography to afford 5-((2-cyanoquinolin-6-yl)methyl)nicotinic acid as a brown solid (250 mg, 80% purity).

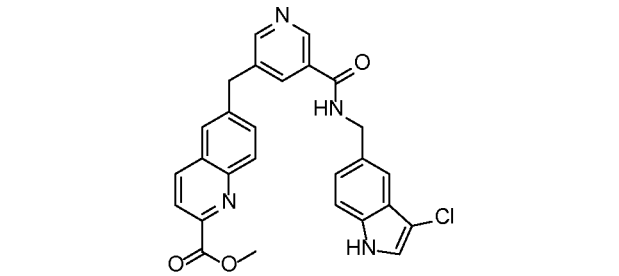


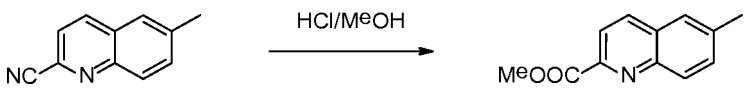
The mixture of 5-((2-cyanoquinolin-6-yl)methyl)nicotinic acid (250 mg, 0.86 mmol, 1.0 eq) and HATU (490 mg, 0.86 mmol, 1.5 eq) in DMF (5 mL) and DIEA (1 mL) was stirred for 1 h, and amine (187 mg, 0.86 mmol, 1.0 eq) was added. The reaction was stirred for 1 h, diluted with DCM, washed with water, and purified via flash chromatography to afford desired as a yellow solid (100 mg, 32%).



To the solution of cyanide (10 mg, 0.22 mmol, 1.0 eq) in DMSO (3 mL) was added K_2CO_3 (30 mg, 0.22 mmol, 1.0 eq), followed by a 30% H_2O_2 (3 mL). The reaction was stirred for 1 h, amine (187 mg, 0.86 mmol, 1.0 eq) was added. The reaction was stirred for 1 h, and quenched with water (5 mL). The precipitate was collected by filtration, rinsed with water, dried and triturated from MeOH then purified via flash chromatography to afford desired as a white solid (52 mg, 50%). LRMS $(M+H)^+$ m/z calculated 470.1, found 470.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.32 (s, 1 H), 9.22 (t, 1 H), 8.92 (s, 1 H), 8.74 (s, 1 H), 8.47 (d, 1 H), 8.25 (s, 1 H), 8.15-8.10 (m, 2 H), 8.05 (d, 1 H), 7.93 (s, 1 H), 7.78-7.75 (m, 2 H), 7.49 (s, 1 H), 7.41 (t, 1 H), 7.36 (d, 1 H), 7.16 (d, 1 H), 4.56 (d, 2 H), 4.29 (s, 2 H).

Example 115: Preparation of methyl 6-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)quinoline-2-carboxylate

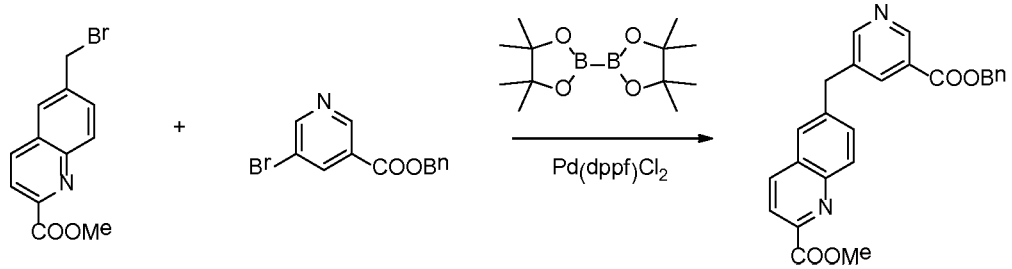




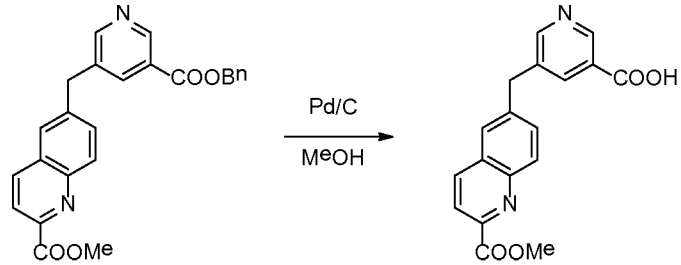
6-methylquinoline-2-carbonitrile (4.7 g, 23.3 mmol, 1.0 eq) was treated with a 25% solution of HCl/MeOH and the mixture was heated to 50 °C and stirred for 4 h, then cooled to rt. After concentration to dryness, the residue was dissolved in DCM, washed with saturated aqueous sodium bicarbonate, water, brine and dried over anhydrous sodium sulfate, and purified via silica column (PE/EA = 10/1) to afford methyl 6-methylquinoline-2-carboxylate as a yellow solid (4.7 g, 33%).



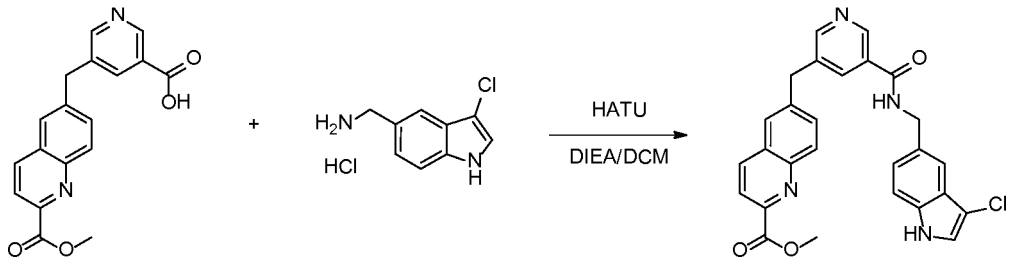
The mixture of methyl 6-methylquinoline-2-carboxylate (4.7 g, 23.3 mmol, 1.0 eq), NBS (4.1 g, 23.3 mmol, 1.0 eq) and AIBN (76 mg, 2 mol%) in tetrachloride carbon (100 mL) was refluxed overnight, then cooled and concentrated to dryness. The residue was purified via silica column (PE/EA = 4/1) to afford methyl 6-(bromomethyl)quinoline-2-carboxylate as a yellow solid (3.9 g, 60%).



The mixture of benzyl 5-bromonictic acid (2.1 g, 7.1 mmol, 1.0 eq), 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4',4',5',5'-tetramethyl-1,3,2-dioxaborolane (1.8 g, 7.1 mmol, 1.0 eq), potassium acetate (2.1 g, 21.3 mmol, 3.0 eq) and (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (105 mg, 2 mol%) in 1,4-dioxane (100 mL) was degassed and stirred at 80 °C overnight, then cooled to rt, methyl 6-(bromomethyl)quinoline-2-carboxylate (2.0 g, 7.1 mmol, 1.0 eq), (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (105 mg, 2 mol%) and an aqueous sodium carbonate (2.3 g, 21.3 mmol, 3.0 eq) in water (25 mL) were added successively. The mixture was degassed, heated to 60 °C and stirred overnight. After cooling, the mixture was filtered through celite, and water (100 mL) and DCM (100 mL) were added to the filtrate. The DCM layer was separated, washed with brine, dried over anhydrous sodium sulfate, and purified on silica gel column to afford methyl 6-((5-((benzyloxy)carbonyl)pyridin-3-yl)methyl)quinoline-2-carboxylate (460 mg, 15%).

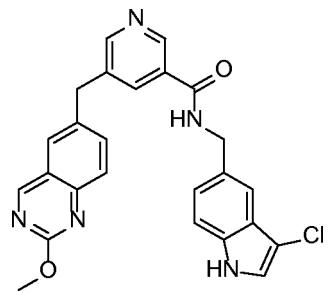


The mixture of methyl 6-((5-((benzyloxy)carbonyl)pyridin-3-yl)methyl)quinoline-2-carboxylate (350 mg, 0.84 mmol, 1.0 eq) and Pd/C (10%, 50 mg) in MeOH (15 mL) was hydrogenated with H_2 balloon overnight. Then it was filtered through celite, rinsed with DCM/MeOH (1/1, 100 mL), and the filtrate was concentrated to dryness to afford 5-((2-(methoxycarbonyl)quinolin-6-yl)methyl)nicotinic acid as a yellow solid (235 mg, 86%).

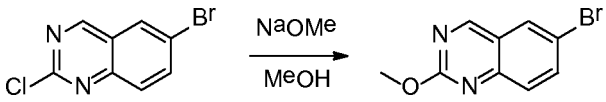


The mixture of 5-((2-(methoxycarbonyl)quinolin-6-yl)methyl)nicotinic acid (150 mg, 0.46 mmol, 1.0 eq), HATU (266 mg, 0.7 mmol, 1.5 eq) in DCM (10 mL) and DIEA (1 mL) was stirred for 15 min, then (3-chloro-1H-indol-5-yl)methanamine hydrochloride (101 mg, 0.46 mmol, 1.0 eq) was added. The reaction was stirred for 2 h, quenched with water. The DCM layer was separated, washed with brine, dried over anhydrous sodium sulfate, and purified on silica gel column to afford methyl 6-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)quinoline-2-carboxylate as a white solid (100 mg, 45%). ^{1}H NMR (DMSO-d6, 300 MHz) δ 11.31 (s, 1 H), 9.22 (t, 1 H), 8.92 (s, 1 H), 8.74 (s, 1 H), 8.52 (d, 1 H), 8.16-8.08 (m, 3 H), 7.95 (s, 1 H), 7.80 (d, 1 H), 7.49 (s, 1 H), 7.41-7.34 (m, 2 H), 7.16 (d, 2 H), 4.29 (s, 2 H), 3.94 (s, 3 H).

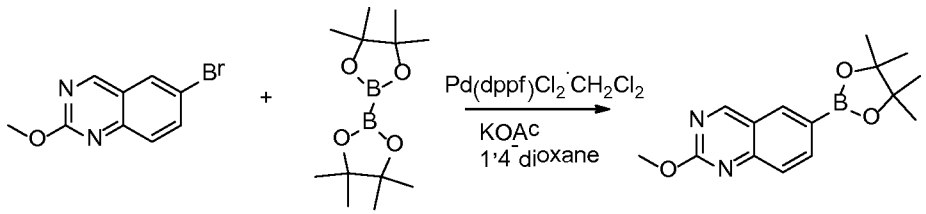
Example 116: Preparation of N-((3-chloro-1H-indol-5-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide



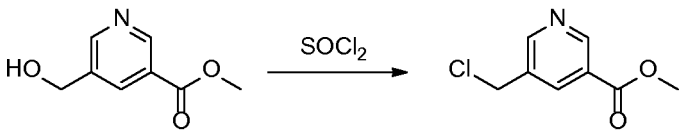
N-((3-chloro-1*H*-indol-5-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide



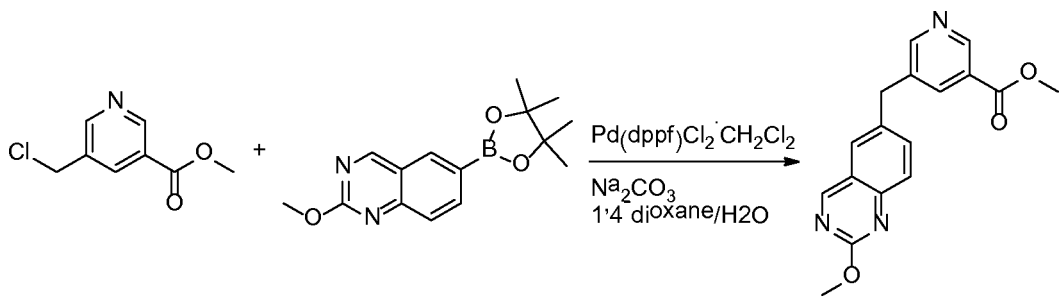
The mixture of 6-bromo-2-chloroquinazoline (2.435 g, 10 mmol, 1 eq) and CH_3ONa (2.75 mg, 51 mmol, 5.1 eq) in MeOH (60 mL) was stirred at 70 °C overnight. After cooling to rt, the solid was filtered, and washed with water to afford the first crop of the product. The filtrate was concentrated and the residue was partitioned between water (50 mL) and DCM (50 mL). The aqueous layer was extracted with DCM (50 mL X 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was combined with the first crop of the product and purified on silica gel column (EA/PE/DCM = 1/6/1, v/v/v) to afford 6-bromo-2-methoxyquinazoline as a light yellow solid (2.30 g, 96.2%).



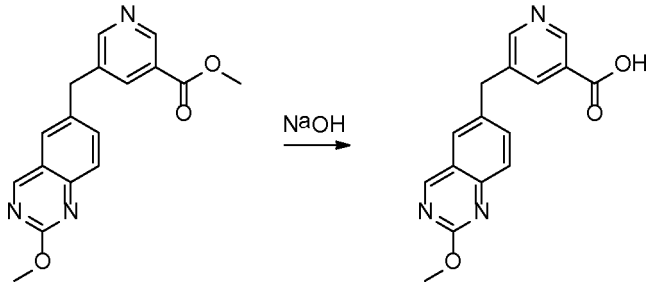
A mixture of 6-bromo-2-methoxyquinazoline (120 mg, 0.50 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (153 mg, 0.6 mmol, 1.2 eq), $Pd(dppf)Cl_2.CH_2Cl_2$ (43 mg, 0.05 mmol, 0.1 eq), KOAc (148 mg, 1.5 mmol, 3 eq) in 1,4-dioxane (5 mL) under N_2 was stirred at 100 °C overnight and concentrated. The residue was purified on silica gel column (EA/PE = 1/6, v/v) to afford 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline as a white solid (150 mg crude, quant)



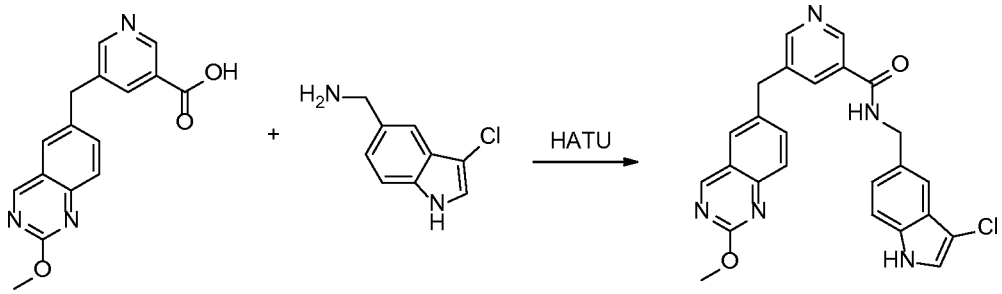
To the solution of methyl 5-(hydroxymethyl)nicotinate (501 mg, 3 mmol, 1 eq) in DCM (10 mL) was added $SOCl_2$ (1 mL). The mixture was stirred at rt overnight and concentrated to afford methyl 5-(chloromethyl)nicotinate hydrochloride as a white solid (660 mg, 99 %).



A mixture of methyl 5-(chloromethyl)nicotinate hydrochloride (1.19 g, 5.36 mmol, 1.0 eq), 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline (2.2 g, 7 mmol, 1.3 eq), $Pd(dppf)Cl_2.CH_2Cl_2$ (590 mg, 0.72 mmol, 0.13 eq), Na_2CO_3 (3.0 g, 28.3 mmol, 5.3 eq) in 1,4-dioxane/H_2O (45 mL/4.5 mL) under N_2 was stirred at 90 °C for 6 h and then filtered. The filtrate was concentrated and the residue was purified via silica column (EA/PE =1/4-1/1, v/v) to afford methyl 5-((2-methoxyquinazolin-6-yl)methyl)nicotinate as a white solid (1.62 g, 97.8%).

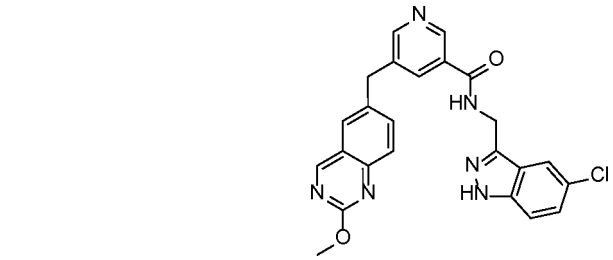


To the solution of methyl 5-((2-methoxyquinazolin-6-yl)methyl)nicotinate (1.62 g, 5.24 mmol, 1 eq) in THF/MeOH (10 mL/5 mL) was added NaOH aqueous solution (1 N, 10 mL). The mixture was stirred at rt overnight and concentrated. The residue was acidified with HCl to pH 2. Filtered and the solid was collected to afford 5-((2-methoxyquinazolin-6-yl)methyl)nicotinic acid as a white solid (1.60 g, 100 %).

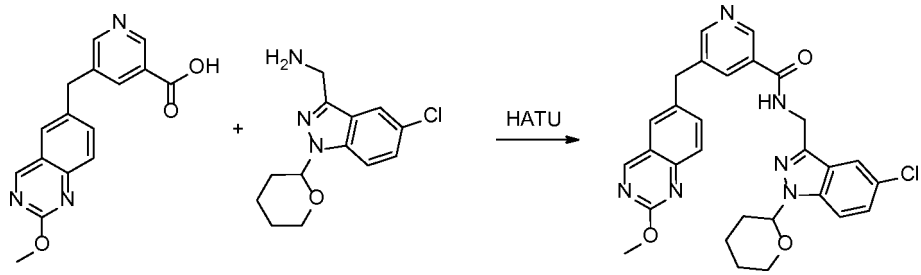


A mixture of 5-((2-methoxyquinazolin-6-yl)methyl)nicotinic acid (64 mg, 0.217 mmol, 1.0 eq), (3-chloro-1H-indol-5-yl)methanamine HCl salt (70 mg, 0.32 mmol, 1.5 eq), HATU (114 mg, 0.30 mmol, 1.4 eq) and DIPEA (1 mL) in DMF (3 mL) was stirred at rt overnight. The mixture was filtered and the filtrate was purified via prep-HPLC to afford N-((3-chloro-1H-indol-5-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide as a yellow solid (40 mg, 40.4%). LRMS ($M+H^+$) m/z calculated 458.1, found 458.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.24 (s, 1 H), 8.89 (d, 1 H), 8.66 (d, 1 H), 8.17 (s, 1 H), 7.86 (s, 1 H), 7.81 (dd, 1 H), 7.76 (d, 1 H), 7.51 (s, 1 H), 7.34 (d, 1 H), 7.24 (s, 1 H), 7.20 (dd, 1 H), 4.67 (s, 2 H), 4.28 (s, 2 H), 4.10 (s, 3 H).

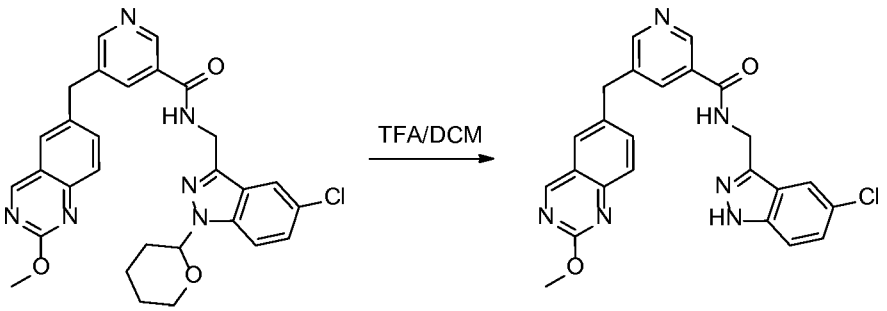
Example 117: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide



N-((5-chloro-1H-indazol-3-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide

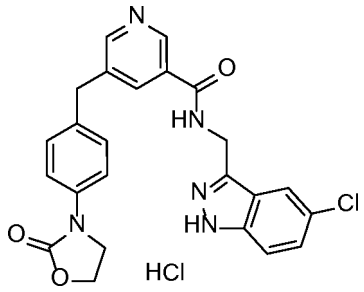


A mixture of 5-((2-methoxyquinazolin-6-yl)methyl)nicotinic acid (295 mg, 1 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (319 mg, 1.2 mmol, 1.2 eq), HATU (456 mg, 1.2 mmol, 1.2 eq) and DIPEA (1 mL) in DMF (5 mL) was stirred at rt overnight. The mixture was filtered and the solid was collected to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide as a white solid (335 mg, 61.8%).



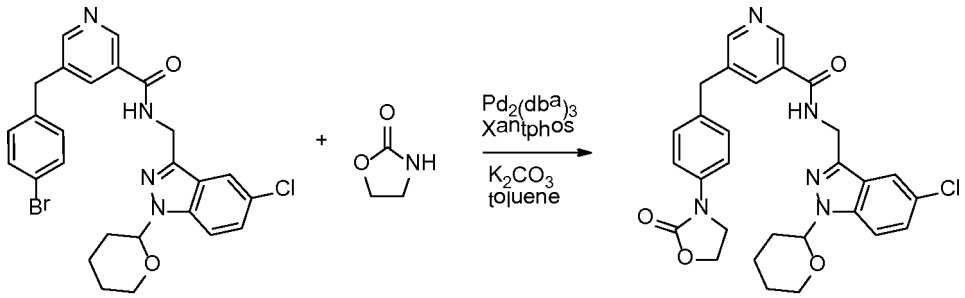
To the solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide (50 mg, 0.09 mmol, 1 eq) in DCM (3 mL) was added TFA (0.5 mL). The mixture was stirred at rt overnight and neutralized with NH_3/MeOH. The mixture was purified via prep-MPLC to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide as a white solid (10 mg, 23.8 %). LRMS ($M+H^+$) m/z calculated 459.1, found 459.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.39 (s, 1 H), 9.31 (s, 1 H), 8.91 (s, 1 H), 8.72 (s, 1 H), 8.12 (s, 1 H), 7.91 (d, 2 H), 7.85 (d, 1 H), 7.75 (d, 1 H), 7.53 (d, 1 H), 7.33 (d, 1 H), 4.78 (d, 2 H), 4.24 (s, 2 H), 4.01 (s, 3 H).

Example 118: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxooxazolidin-3-yl)benzyl)nicotinamide

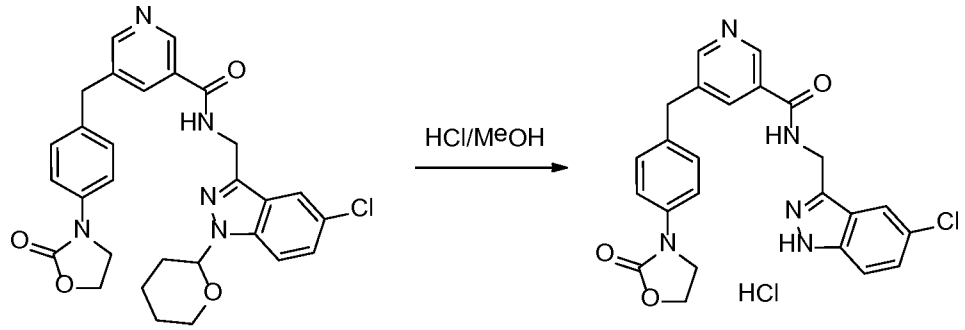


HCl

N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(4-(2-oxooxazolidin-3-yl)benzyl)nicotinamide hydrochloride

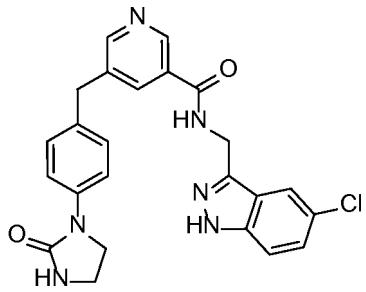


A mixture of 5-(4-bromobenzyl)-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide (108 mg, 0.20 mmol, 1.0 eq), oxazolidin-2-one (56 mg, 0.64 mmol, 3.2 eq), $Pd_2(dba)_3$ (22 mg, 0.024 mmol, 0.12 eq), Xantphos (26 mg, 0.044 mmol, 0.22 eq), K_2CO_3 (108 mg, 0.78 mmol, 3.9 eq) in toluene (5 mL) under N_2 was stirred at 100 °C overnight and concentrated. The residue was purified via prep-MPLC to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(2-oxooxazolidin-3-yl)benzyl)nicotinamide as a white solid (42 mg, 38.5%)

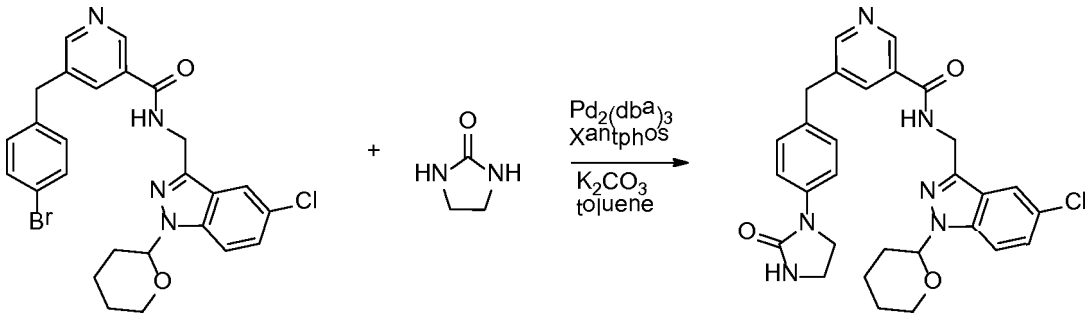


The mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(2-oxooxazolidin-3-yl)benzyl)nicotinamide (42 mg, 0.077 mmol, 1 eq) in HCl/EA (5 N, 4 mL) was stirred at rt overnight. The precipitate was collected by suction to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxooxazolidin-3-yl)benzyl)nicotinamide hydrochloride as a white solid (23 mg, 60.5%). LRMS ($M+H^+$) m/z calculated 462.1, found 462.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.31 (s, 1 H), 9.49 (t, 1 H), 9.01 (d, 1 H), 8.78 (d, 1 H), 8.38 (s, 1 H), 7.92 (d, 1 H), 7.55-7.49 (m, 3 H), 7.35-7.30 (m, 3 H), 4.80 (d, 2 H), 4.41 (t, 2 H), 4.09 (s, 2 H), 4.02 (t, 2 H).

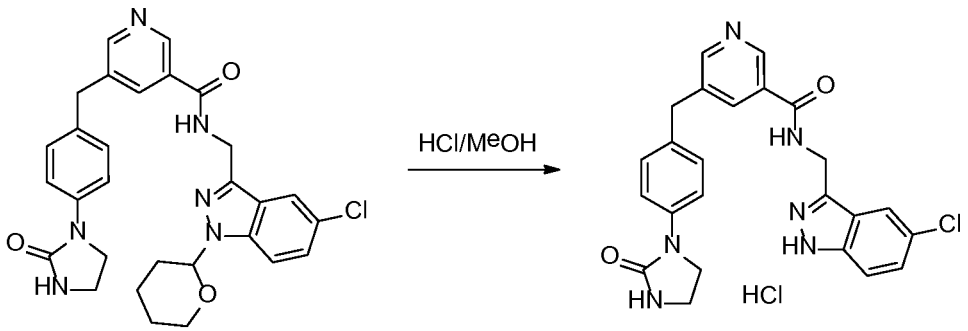
Example 119: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxoimidazolidin-1-yl)benzyl)nicotinamide



N-((5-chloro-1*H*-indazol-3-yl)methyl)-5-(4-(2-oxoimidazolidin-1-yl)benzyl)nicotinamide hydrochloride

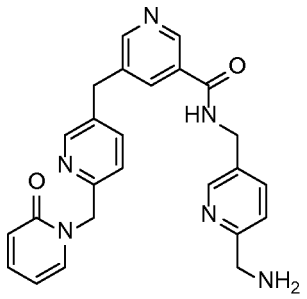


A mixture of 5-(4-bromobenzyl)-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide (108 mg, 0.20 mmol, 1.0 eq), imidazolidin-2-one (86 mg, 1.0 mmol, 5 eq), $Pd_2(dba)_3$ (24 mg, 0.024 mmol, 0.12 eq), Xantphos (31 mg, 0.054 mmol, 0.27 eq), K_2CO_3 (138 mg, 1.0 mmol, 5 eq) in toluene (5 mL) under N_2 was stirred at 100 °C overnight and concentrated. The residue was purified via prep-MPLC to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(2-oxoimidazolidin-1-yl)benzyl)nicotinamide as a white solid (26 mg, 23.9%)

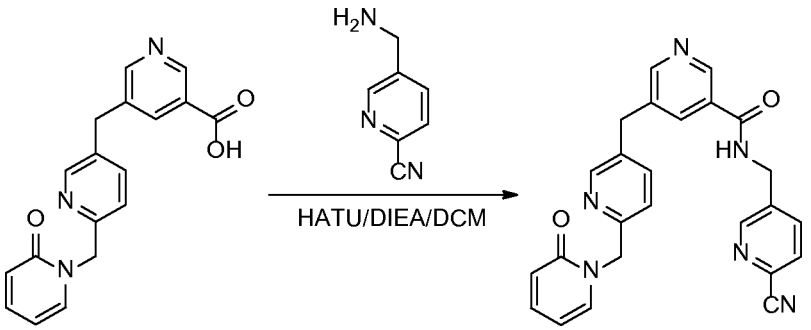


The mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(2-oxoimidazolidin-1-yl)benzyl)nicotinamide (26 mg, 0.048 mmol, 1 eq) in HCl/EA (5 N, 2 mL) and MeOH (2 mL) was stirred at rt overnight. The volatiles were concentrated to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxoimidazolidin-1-yl)benzyl)nicotinamide hydrochloride as a yellow solid (20 mg, 84.3%). LRMS ($M+H^+$) m/z calculated 461.1, found 461.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.16 (s, 1 H), 8.89 (s, 1 H), 8.87 (s, 1 H), 7.91 (d, 1 H), 7.54 (d, 2 H), 7.52 (d, 1 H), 7.39 (dd, 1 H), 7.29 (d, 2 H), 4.98 (s, 2 H), 4.27 (s, 2 H), 3.96 (t, 2 H), 3.56 (t, 2 H).

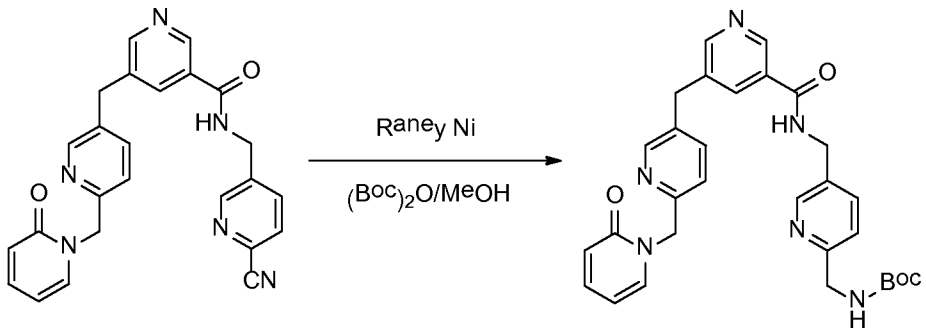
Example 120: Preparation of N-((6-(aminomethyl)pyridin-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide



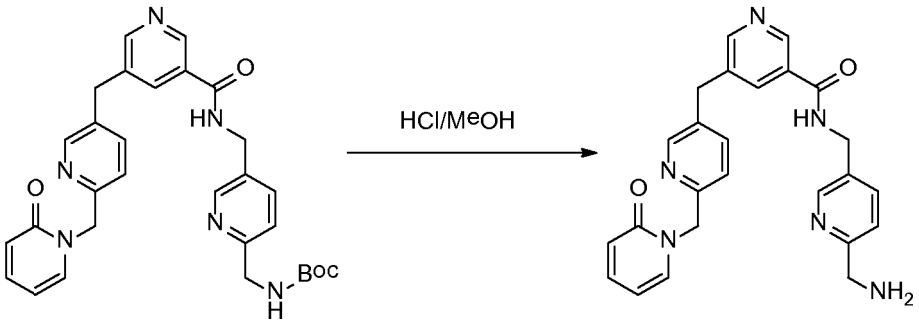
N-((6-(aminomethyl)pyridin-3-yl)methyl)-5-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)nicotinamide



A mixture of 5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinic acid (70 mg, 0.21 mmol, 1.0 eq), 5-(aminomethyl)picolinonitrile HCl salt (45 mg, 0.21 mmol, 1.0 eq), HATU (83 mg, 0.21 mmol, 1.0 eq) and DIEA (0.5 mL) in DCM (10 mL) was stirred at rt for 3 h. The mixture was evaporated under reduced pressure to give an oil, which was purified by flash chromatography (MeCN/H_2O = 1/4 to 2/1) to afford N-((6-cyanopyridin-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide as white solid (82 mg, 86%).

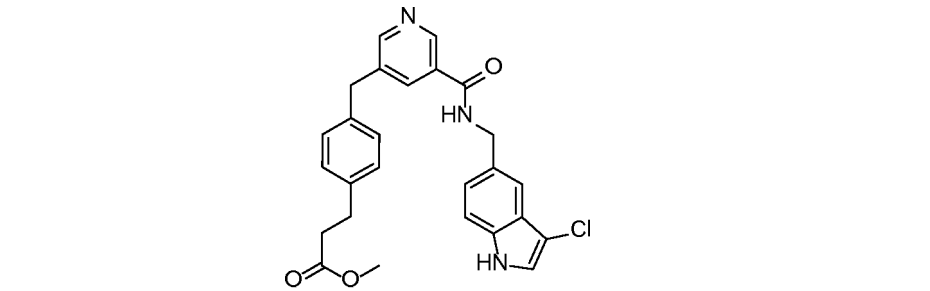


N-((6-Cyanopyridin-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide (80 mg, 0.18 mmol, 1.0 eq) and $(Boc)_2O$ (120 mg, 0.55 mmol, 3.0 eq) was dissolved in 10 mL of methanol, combined with 50 mg Raney nickel and hydrogenated at rt for 2 h at a pressure of 1 atm. Then the catalyst was filtered off and the filtrate was concentrated under reduced pressure to give *tert*-butyl ((5-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)pyridin-2-yl)methyl)carbamate (46 mg, 46%).

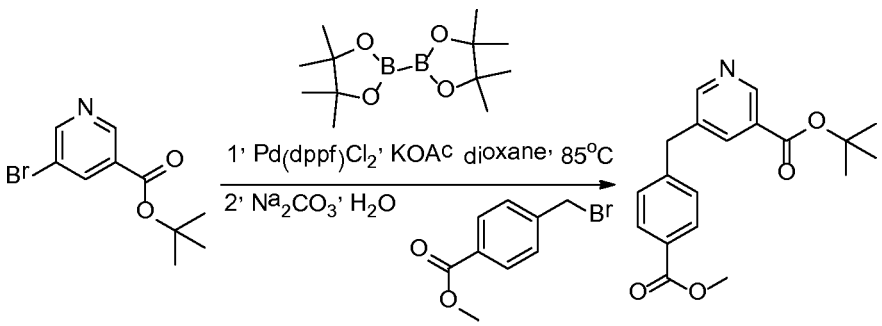


A solution of *tert*-butyl ((5-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)pyridin-2-yl)methyl)carbamate (46 mg, 0.085 mmol, 1.0 eq) in MeOH (3 mL) and HCl/MeOH (3 N, 2 mL) was stirred at rt for 2 h. Then the mixture was concentrated. The residue was recrystallized with MeOH/EtOAc to afford N-((6-(aminomethyl)pyridin-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide as a white solid (29 mg, 72%). LRMS ($M+H^+$) m/z calculated 441.2, found 441.2. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.87 (t, 1 H), 9.14 (s, 1 H), 8.93 (d, 1 H), 8.72 (s, 1 H), 8.64 (s, 1 H), 8.53 (br, 3 H), 8.06 (d, 1 H), 7.92 (dd, 1 H) , 7.86 (dd, 1 H), 7.55 (d, 1 H), 7.47 (m, 1 H), 7.37 (d, 1 H), 6.39 (d, 1 H), 6.31-6.27 (m, 1 H), 5.27 (s, 2 H), 4.54 (d, 2 H), 4.24 (s, 2 H), 4.18 (m, 2 H).

Example 121: Preparation of methyl 3-(4-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)propanoate

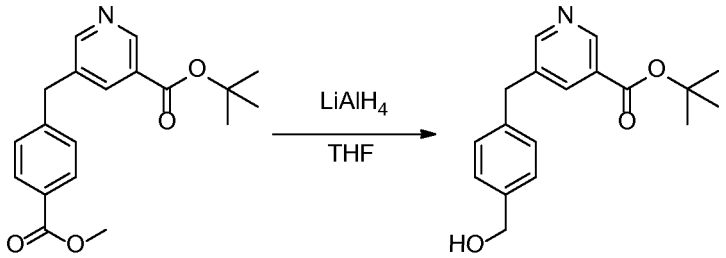


methyl 3-(4-((5-(((3-chloro-1*H*-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)propanoate

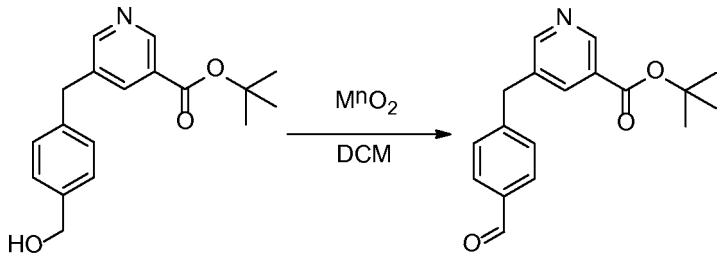


To a solution of *tert*-butyl 5-bromonicotinate (5.0 g, 19.4 mmol, 1.0 eq) in 1,4-dioxane (200 mL) were added KOAc (5.7 g, 58.2 mmol, 3.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.93 g, 19.4 mmol, 1.0 eq) and $Pd(dppf)Cl_2$ (355 mg, 0.49 mmol, 0.03 eq). The mixture was heated at 85 °C overnight under N_2, and then the mixture was cooled to rt. To the mixture were added methyl 4-(bromomethyl)benzoate (4.44 g, 19.4 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (355 mg, 0.49 mmol, 0.03 eq) and Na_2CO_3 (6.17 g, 58.2 mmol, 3.0 eq) in water (40 mL). The mixture was heated to 80 °C overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (100 mL) and extracted with EA (100 mL x 3).

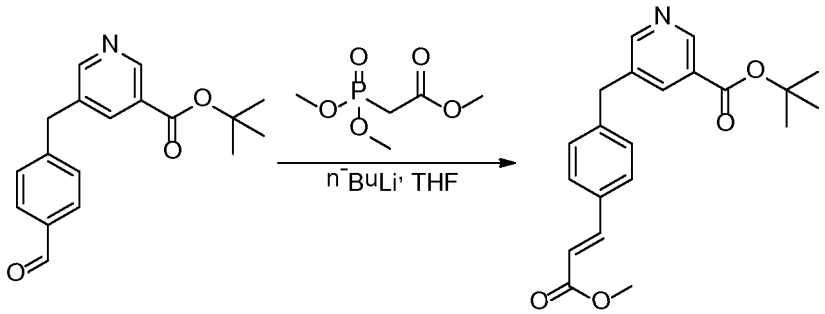
The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (PE/EA = 10/1 to 4/1) to afford *tert*-butyl 5-(4-(methoxycarbonyl)benzyl)nicotinate as a yellow solid (3.8 g, 60%).



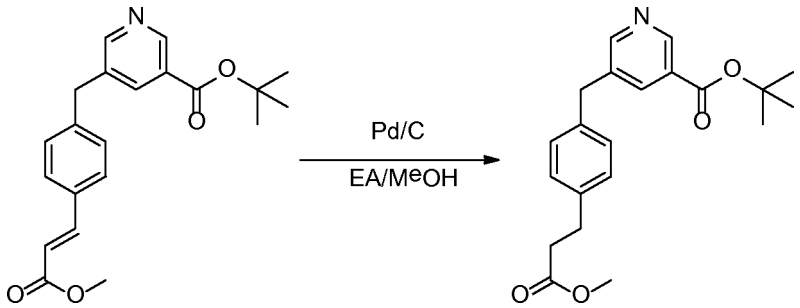
To a solution of *tert*-butyl 5-(4-(methoxycarbonyl)benzyl)nicotinate (3.8 g, 11.6 mmol, 1.0 eq) in THF (80 mL) was added $LiAlH_4$ (441 mg, 11.6 mmol, 1.0 eq) at -78 °C under N_2. The mixture was stirred at rt overnight. The mixture was added $Na_2SO_4.10H_2O$ to work up at -78 °C. The mixture was stirred warm to rt. The mixture was filtered. The filter cake was washed with EA (30 mL x 2). The filtrate was concentrated. The residue was purified on silica gel column (PE/EA = 10/1 to 3/1) to afford *tert*-butyl 5-(4-(hydroxymethyl)benzyl)nicotinate as a yellow solid (2.0 g, 58%).



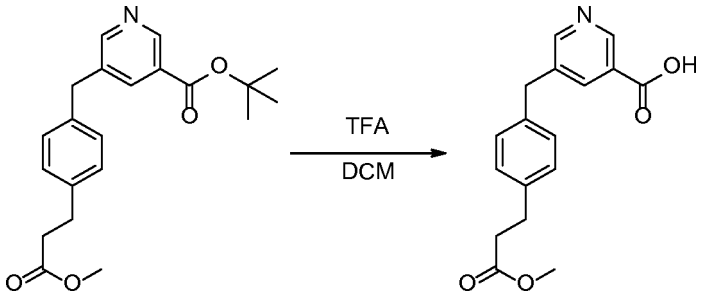
To a solution of *tert*-butyl 5-(4-(hydroxymethyl)benzyl)nicotinate (700 mg, 2.34 mmol, 1.0 eq) in DCM (7 mL) were added MnO_2 (2.0 g, 23.4 mmol, 10.0 eq). The suspension was stirred at rt overnight. The mixture was filtered on a short silica gel column, and washed with (DCM/MeOH = 20 mL/20 mL). The filtrate was concentrated to afford *tert*-butyl 5-(4-formylbenzyl)nicotinate as a white solid (700 mg crude, quant).



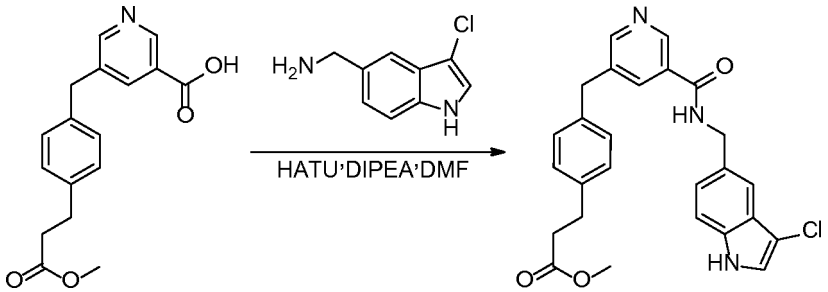
To a solution of methyl 2-(dimethoxyphosphoryl)acetate (450 mg, 2.47 mmol, 1.05 eq) in THF (7 mL) was added dropwise *n*-BuLi (1.1 mL, 2.5 M, 2.7 mmoL, 1.15 eq) at -78 °C under N_2. The mixture was stirred at -78 °C for 30 min. *tert*-butyl 5-(4-formylbenzyl)nicotinate (700 mg, 2.36 mmol, 1.0 eq) in THF (5 mL) was added dropwise into the mixture. The mixture was stirred at rt overnight. The mixture was work up with water (2 mL) at 0 °C, saturated $NaHCO_3$ (5 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to afford (E)-*tert*-butyl 5-(4-(3-methoxy-3-oxoprop-1-en-1-yl)benzyl)nicotinate as a white solid (880 mg, 95%).



To a solution of (E)-*tert*-butyl 5-(4-(3-methoxy-3-oxoprop-1-en-1-yl)benzyl)nicotinate (880 mg, 2.49 mmol, 1.0 eq) in EA (8 mL) and MeOH (4 mL) was added Pd/C (170 mg, 10%Pd). The mixture was hydrogenated at rt for 4 h. The mixture was filtered and the filtered cake was washed with DCM (10 mL) and MeOH (10 mL). The filtrate was concentrated to dryness under reduced pressure to afford *tert*-butyl 5-(4-(3-methoxy-3-oxopropyl)benzyl)nicotinate as a white solid (820 mg, 93%).

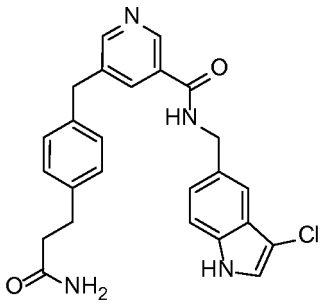


To a solution of *tert*-butyl 5-(4-(3-methoxy-3-oxopropyl)benzyl)nicotinate (820 mg, 2.31 mmol, 1.0 eq) in TFA (4 mL) and DCM (8 mL). The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure to afford 5-(4-(3-methoxy-3-oxopropyl)benzyl)nicotinic acid as a brown oil (1.5 g crude, quant).

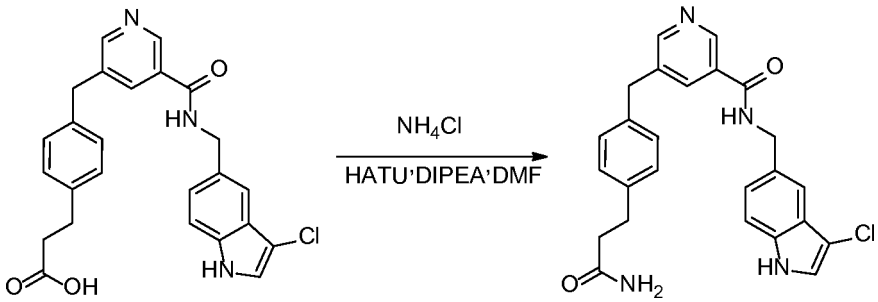


To a solution of 5-(4-(3-methoxy-3-oxopropyl)benzyl)nicotinic acid (750 mg crude, 1.16 mmol, 1.0 eq) in DMF (4 mL) were added DIPEA (1.5 g, 11.6 mmol, 10.0 eq) and HATU (529 mg, 1.39 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (3-chloro-1H-indol-5-yl)methanamine (251 mg, 1.16 mmol, 1.0 eq) was then added and the mixture was stirred at rt for 2 h under N_2. The mixture was mixed with water (10 mL) and extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford methyl 3-(4-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)propanoate as an off-white solid (400 mg, 75%). LRMS ($M+H^+$) m/z caculated 462.1, found 462.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.32 (brs, 1 H), 9.20 (t, 1 H), 8.88 (d, 1 H), 8.62 (d, 1 H), 8.05 (d, 1 H), 7.50 (d, 1 H), 7.42 (s, 1 H), 7.37 (d, 1 H), 7.20-7.10 (m, 5 H), 4.56 (d, 2 H), 3.98 (s, 2 H), 3.55 (s, 3 H), 2.80 (t, 2 H), 2.58 (t, 2 H).

Example 122: Preparation of 5-(4-(3-amino-3-oxopropyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide

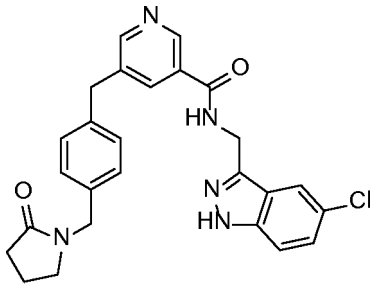


5-(4-(3-amino-3-oxopropyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide

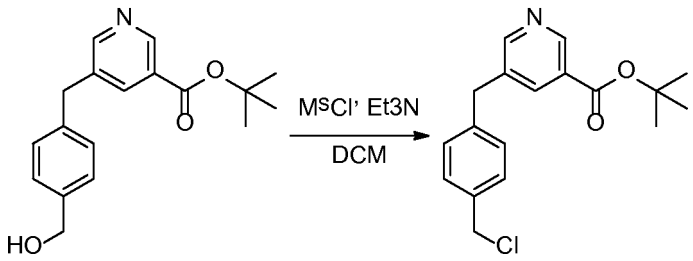


To a solution of 3-(4-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)propanoic acid (280 mg crude, 0.38 mmol, 1.0 eq) in DMF (3 mL) were added DIPEA (245 mg, 1.9 mmol, 5.0 eq) and HATU (173 mg, 0.46 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, NH_4Cl (102 mg, 1.9 mmol, 5.0 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was purified via flash chromatography to afford 5-(4-(3-amino-3-oxopropyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide as a white solid (75 mg, 44%). LRMS ($M+H^+$) m/z caculated 447.1, found 447.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.33 (brs, 1 H), 9.20 (t, 1 H), 8.88 (d, 1 H), 8.62 (d, 1 H), 8.05 (s, 1 H), 7.50 (d, 1 H), 7.42 (s, 1 H), 7.37 (d, 1 H), 7.26 (brs, 1 H), 7.20-7.10 (m, 5 H), 6.74 (brs, 1 H), 4.56 (d, 2 H), 3.98 (s, 2 H), 2.74 (t, 2 H), 2.30 (t, 2 H).

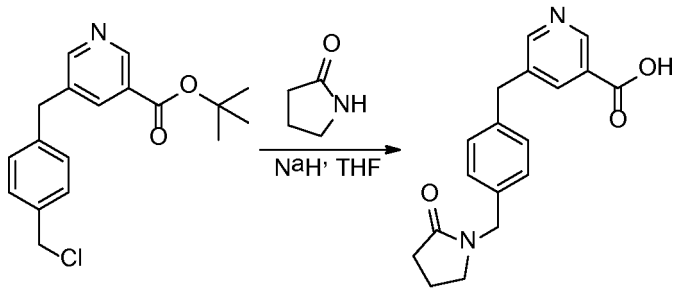
Example 123: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinamide



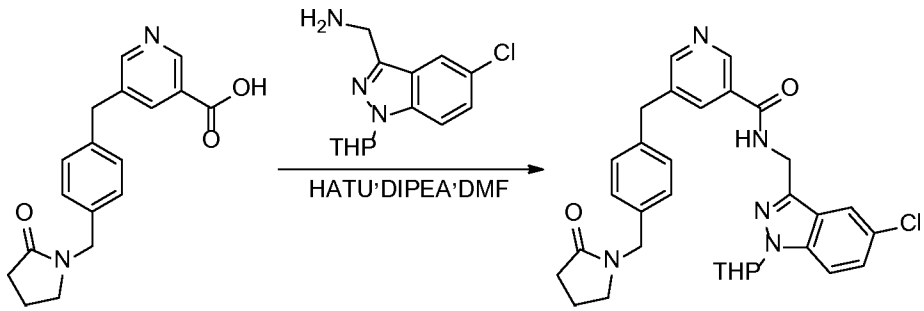
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinamide



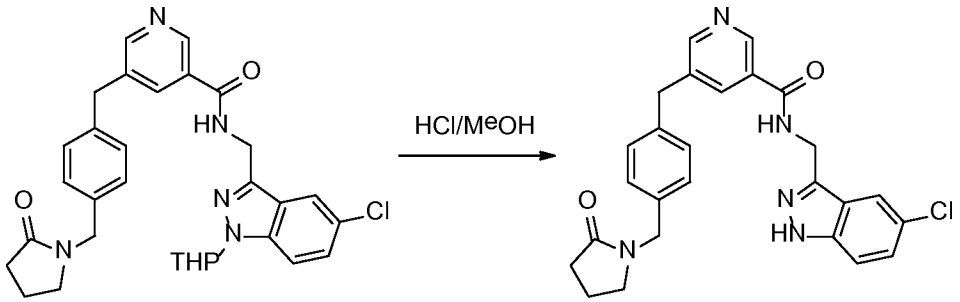
To a solution of *tert*-butyl 5-(4-(hydroxymethyl)benzyl)nicotinate (300 mg, 1.0 mmol, 1.0 eq) in DCM (3 mL) were added Et_3N (303 mg, 3.0 mmol, 3.0 eq) and MsCl (127 mg, 1.1 mmol, 1.1 eq) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with saturated $NaHCO_3$ (5 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford *tert*-butyl 5-(4-(chloromethyl)benzyl)nicotinate as a white solid (140 mg, 38%).



To a solution of pyrrolidin-2-one (224 mg, 2.64 mmol, 6.0 eq) in THF (4 mL) were added NaH (53 mg, 1.32 mmol, 3.0 eq) at 0 °C under N_2. The suspension was stirred at 0 °C for 15 min, then *tert*-butyl 5-(4-(chloromethyl)benzyl)nicotinate (140 mg, 0.44 mmol, 1.0 eq) was added into the mixture. The mixture was stirred at rt overnight. The reaction mixture was poured into ice-water (5 mL), acidified with 1 N HCl to pH 2-3, and concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford 5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinic acid as a white solid (50 mg, 37%).

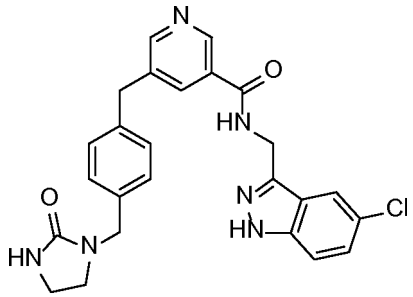


To a solution of 5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinic acid (50 mg, 0.16 mmol, 1.0 eq) in DMF (2 mL) were added DIPEA (103 mg, 0.8 mmol, 5.0 eq) and HATU (73 mg, 0.19 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (43 mg, 0.16 mmol, 1.0 eq) was then added and the mixture was stirred at rt for 2 h under N_2. The mixture was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinamide as a white solid (70 mg, 79%).

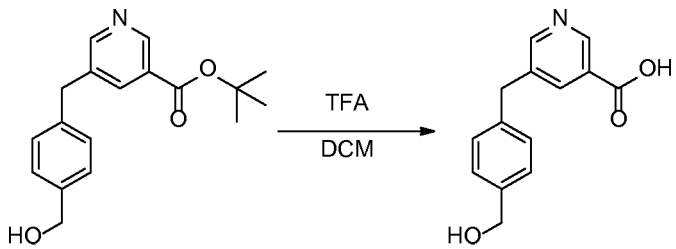


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinamide (70 mg, 0.13 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/MeOH (2 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (5 mL), neutralized with saturated $NaHCO_3$ (10 mL) and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinamide as a white solid (34 mg, 58%). LRMS ($M+H^+$) m/z caculated 474.1, found 474.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.07 (brs, 1 H), 9.29 (t, 1 H), 8.87 (d, 1 H), 8.63 (d, 1 H), 8.06 (s, 1 H), 7.90 (d, 1 H), 7.53 (d, 1 H), 7.33 (dd, 1 H), 7.23 (d, 2 H), 7.13 (d, 2 H), 4.78 (d, 2 H), 4.30 (s, 2 H), 4.00 (s, 2 H), 3.18 (t, 2 H), 2.47 (t, 2 H), 2.00-1.80 (m, 2 H).

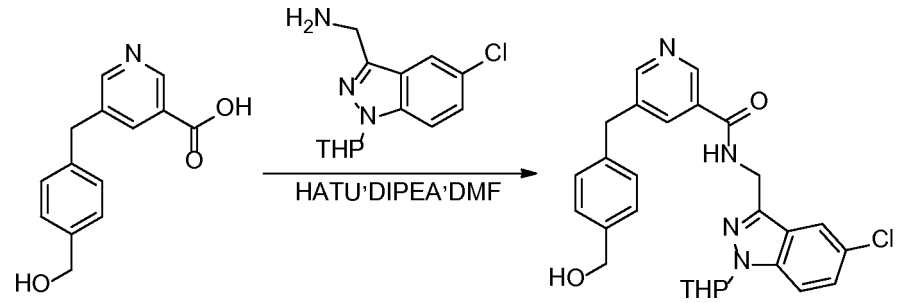
Example 124: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)nicotinamide



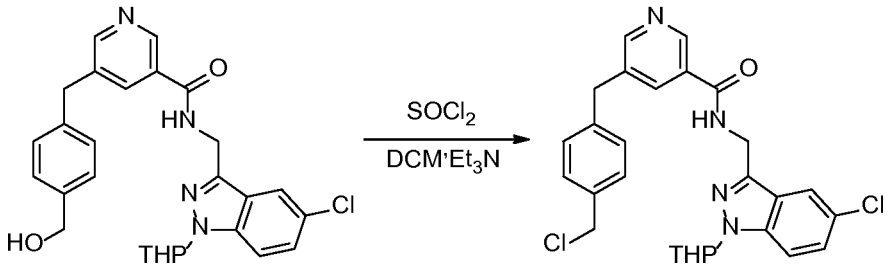
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)nicotinamide



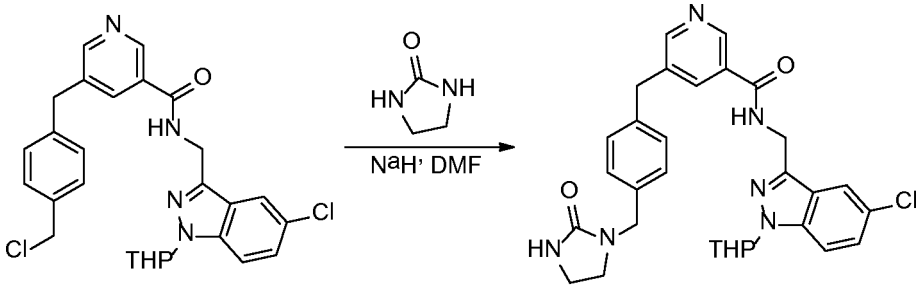
A solution of *tert*-butyl 5-(4-(hydroxymethyl)benzyl)nicotinate (1.7 g, 5.69 mmol, 1.0 eq) in TFA (4 mL) and DCM (20 mL) was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was purified via flash chromatography to afford 5-(4-(hydroxymethyl)benzyl)nicotinic acid as a white solid (1.18 g, 86%).



To a solution of 5-(4-(hydroxymethyl)benzyl)nicotinic acid (1.18 g, 4.86 mmol, 1.0 eq) in DMF (10 mL) were added DIPEA (3.13 g, 24.3 mmol, 5.0 eq) and HATU (2.22 g, 5.83 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (1.29 g, 4.86 mmol, 1.0 eq) was then added and the mixture was stirred at rt for 2 h under N_2. The mixture was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(hydroxymethyl)benzyl)nicotinamide as a white solid (1.9 g, 80%).

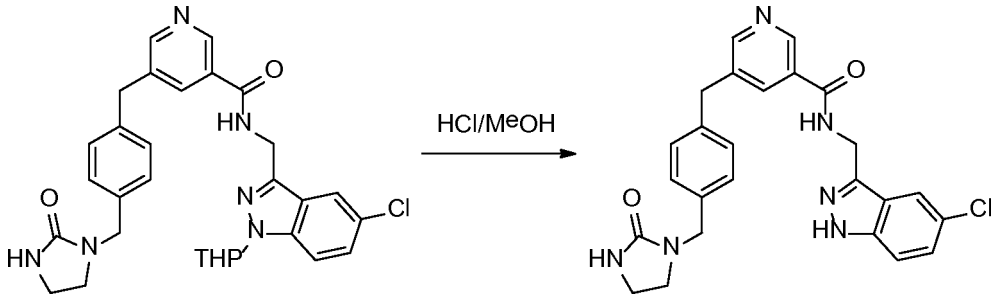


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(hydroxymethyl)benzyl)nicotinamide (1.9 g, 3.87 mmol, 1.0 eq) in DCM (38 mL) were added Et_3N (1.17 g, 11.6 mmol, 3.0 eq) and $SOCl_2$ (4.6 g, 38.7 mmol, 10.0 eq) at 0 °C. The mixture was stirred at rt for 2 h. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with saturated $NaHCO_3$ (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(chloromethyl)benzyl)nicotinamide as a white solid (500 mg, 25%).



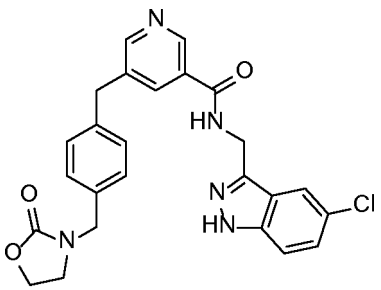
To a solution of imidazolidin-2-one (101 mg, 1.18 mmol, 6.0 eq) in DMF (2 mL) were added NaH (24 mg, 60% in oil, 0.59 mmol, 3.0 eq) at 0 °C under N_2. The suspension was stirred at 0 °C for 30 min. Then N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(chloromethyl)benzyl)nicotinamide (100 mg, 0.2 mmol, 1.0 eq) was added into the mixture. The mixture was stirred at rt overnight. The reaction mixture was poured into ice-water (5 mL), extracted with EA (10 mL X 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via

flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)nicotinamide as a white solid (20 mg, 18%).

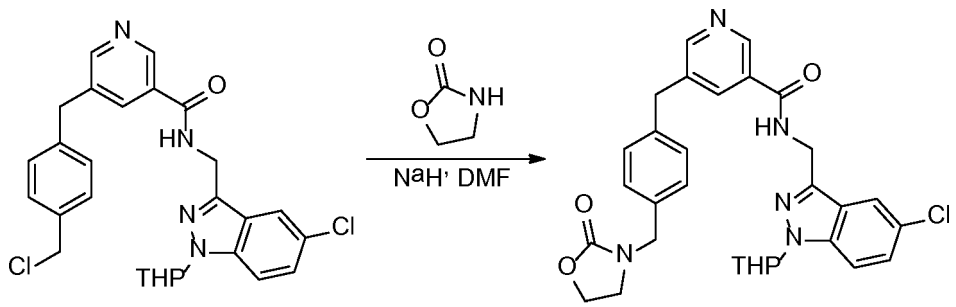


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)nicotinamide (20 mg, 0.036 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/MeOH (2 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (5 mL), neutralized with saturated $NaHCO_3$ (5 mL) and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)nicotinamide as a white solid (17 mg, quant). LRMS ($M+H^+$) m/z caculated 475.1, found 475.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.09 (brs, 1 H), 9.30 (t, 1 H), 8.87 (d, 1 H), 8.63 (d, 1 H), 8.07 (s, 1 H), 7.91 (d, 1 H), 7.53 (d, 1 H), 7.33 (d, 1 H), 7.25-7.15 (m, 4 H), 6.39 (brs, 1 H), 4.78 (d, 2 H), 4.17 (s, 2 H), 4.00 (s, 2 H), 3.18-3.15 (m, 4 H).

Example 125: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide

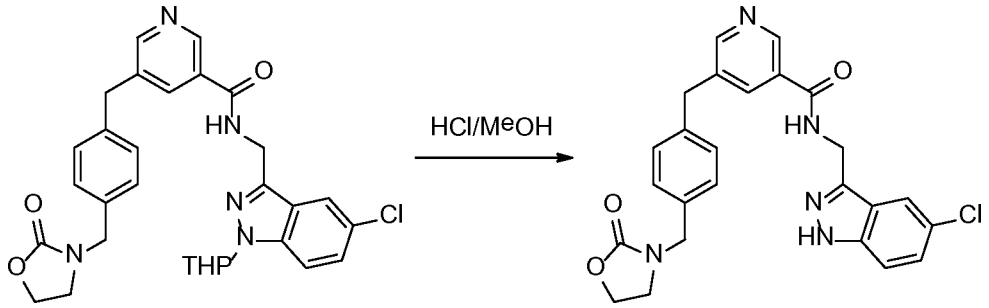


N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide



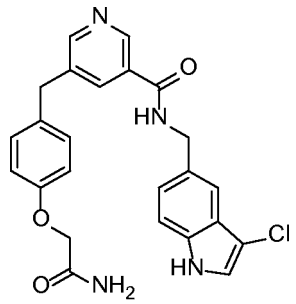
To a solution of oxazolidin-2-one (102 mg, 1.18 mmol, 6.0 eq) in DMF (2 mL) were added NaH (24 mg, 60% in oil, 0.59 mmol, 3.0 eq) at 0 °C under N_2. The suspension was stirred at 0 °C for 30 min. Then N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-(chloromethyl)benzyl)nicotinamide (100 mg, 0.2 mmol, 1.0 eq) was added into the mixture. The mixture was stirred at rt overnight. The reaction mixture was poured into ice-water (5 mL), extracted with EA (10 mL x 3). The combined organic layers were washed with

brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide as a white solid (60 mg, 55%).

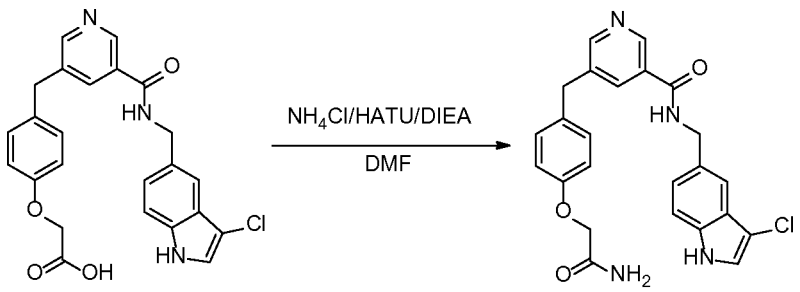


To a solution of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide (60 mg, 0.11 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/MeOH (2 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (5 mL), neutralized with saturated $NaHCO_3$ (5 mL) and concentrated. The residue was purified via flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide as a white solid (47 mg, 92%). LRMS ($M+H^+$) m/z caculated 476.1, found 476.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.09 (brs, 1 H), 9.30 (t, 1 H), 8.88 (d, 1 H), 8.64 (d, 1 H), 8.07 (s, 1 H), 7.91 (d, 1 H), 7.55-7.50 (m, 1 H), 7.40-7.20 (m, 5 H), 4.78 (d, 2 H), 4.30-4.20 (m, 4 H), 4.00 (d, 2 H), 3.37 (s, 2 H).

Example 126: Preparation of 5-(4-(2-amino-2-oxoethoxy)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



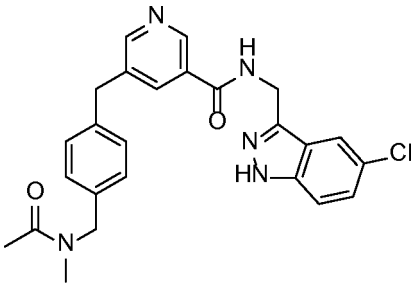
5-(4-(2-amino-2-oxoethoxy)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



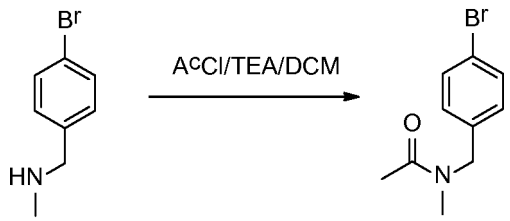
A mixture of 2-(4-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenoxy)acetic acid (75 mg, 0.17 mmol, 1.0 eq), NH_4Cl (11 mg, 0.2 mmol, 1.2 eq), HATU (97 mg, 0.26 mmol, 1.5 eq) and DIEA (66 mg, 0.51 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified by flash chromatography to afford 5-(4-(2-amino-2-oxoethoxy)benzyl)-N-((3-chloro-1H-indol-5-

yl)methyl)nicotinamide as a white solid (10.8 mg, 14%).LRMS ($M+H^+$) m/z calculated 449.14, found 449.1. ^1H NMR (DMSO-*d*6, 400 MHz) δ 11.33 (s, 1 H), 9.20 (t, 1 H), 8.87 (s, 1 H), 8.61 (s, 1 H), 8.04 (s, 1 H), 7.50 (s, 1 H), 7.47 (s, 1 H), 7.42 (s, 1 H), 7.38-7.36 (m, 2 H), 7.20-7.16 (m, 3 H), 6.87 (d, 2 H), 4.56 (d, 2 H), 4.37 (s, 2 H), 3.96 (s, 2 H).

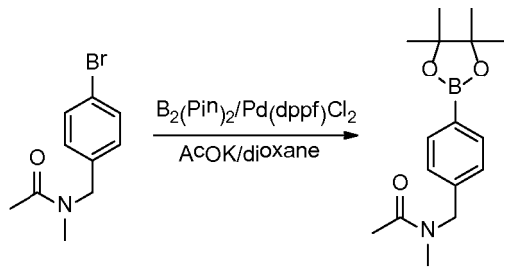
Example 127: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide



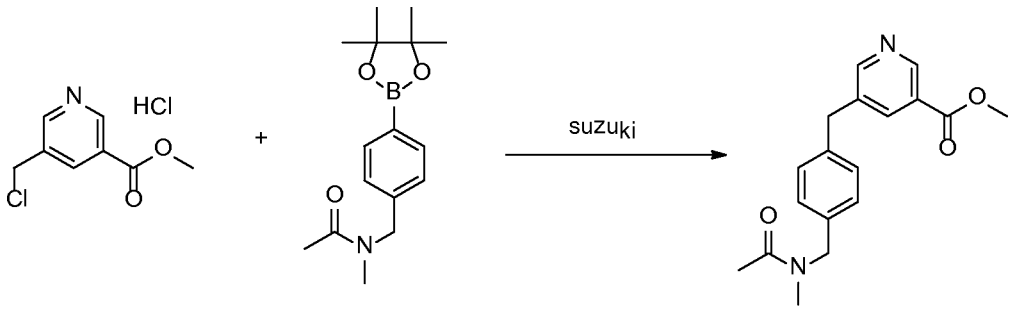
N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide



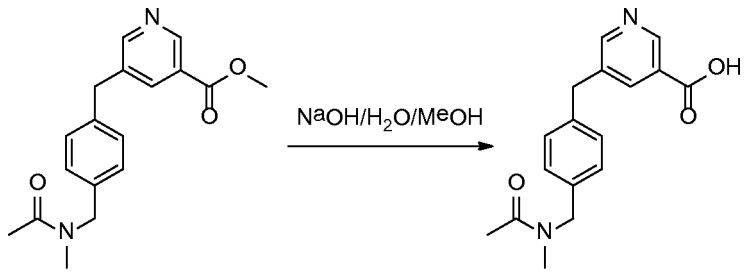
A mixture of 1-(4-bromophenyl)-N-methylmethanamine (2 g, 10 mmol, 1.0 eq), TEA (3 g, 30 mmol, 3 eq) was cooled to 0 °C. Then acetyl chloride (942 mg, 12 mmol, 1.2 eq) in DCM (20 mL) was added. The mixture was stirred at rt for 1 h. The mixture was washed with brine,dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel column (PE/EtOAc = 5/1) to give N-(4-bromobenzyl)-N-methylacetamide as a yellow oil (1.6 g, 67%).



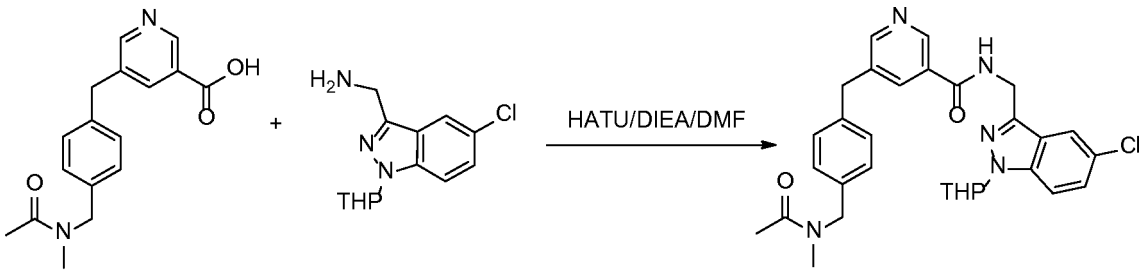
The mixture of N-(4-bromobenzyl)-N-methylacetamide (872 mg, 3.6 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (914 mg, 3.6 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (131 mg, 5%) and KOAc (1 g, 10.8 mmol, 3.0 eq) in dioxane (20 mL) was degassed with N_2 and stirred at 85 °C overnight. Then the mixture was concentrated. The residue was diluted with EtOAc (100 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified via flash chromatography (PE/EtOAc = 5/1) to afford N-methyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)acetamide as a yellow solid (750 mg, 75%).



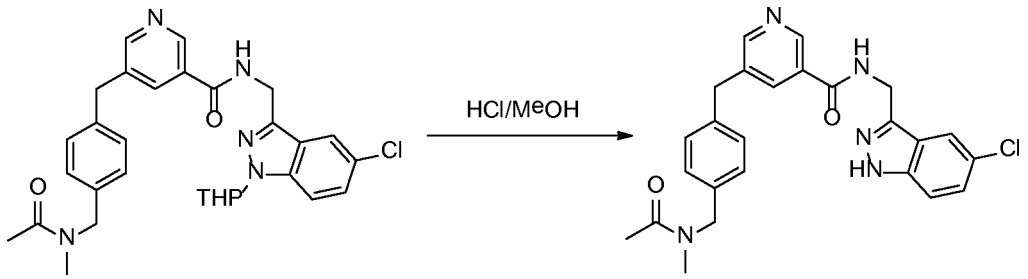
The mixture of methyl 5-(chloromethyl)nicotinate HCl salt (577 mg, 2.6 mmol, 1.0 eq), N-methyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)acetamide (750 mg, 2.6 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (95 mg, 0.05 eq) and Na_2CO_3 (827 mg, 7.8 mmol, 3.0 eq, solution in 10 mL of water) in 1,4-dioxane (20 mL) was degassed with N_2 and stirred at 95 °C overnight. Then the mixture was cooled and concentrated. The residue was dissolved in EtOAc (150 mL), washed with water, brine and dried over anhydrous sodium sulfate, filtered and purified on silica gel column (PE/EtOAc = 1/2) to afford methyl 5-(4-((N-methylacetamido)methyl)benzyl)nicotinate as a brown oil (300 mg, 27%).



To a solution of methyl 5-(4-((N-methylacetamido)methyl)benzyl)nicotinate (300 mg, 0.96 mmol, 1.0 eq) in MeOH (3 mL) and H_2O (3 mL) was added NaOH (115 mg, 2.88 mmol, 3.0 eq). The mixture was stirred at rt for 1 h. Then the organic solvents were evaporated. The residue was neutralized with 1 N HCl. The obtained mixture was concentrated to afford 5-(4-((N-methylacetamido)methyl)benzyl)nicotinic acid as a yellow solid (454 mg, crude, contained NaCl).

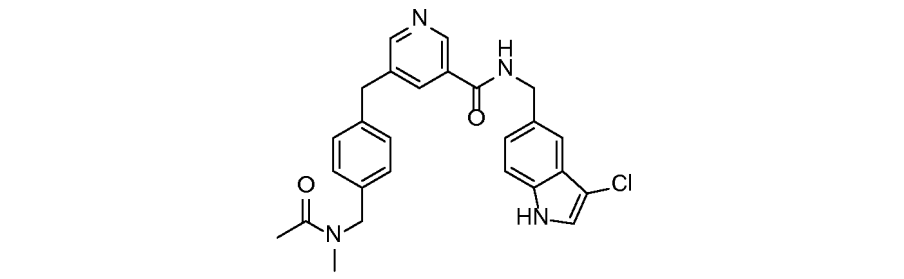


A mixture of 5-(4-((N-methylacetamido)methyl)benzyl)nicotinic acid (277 mg, crude, 0.48 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (127 mg, 0.48 mmol, 1.0 eq), HATU (274 mg, 0.72 mmol,1.5 eq) and DIEA (185 mg, 1.44 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified directly by flash chromatography to afford N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide as a yellow oil (158 mg, 60%).

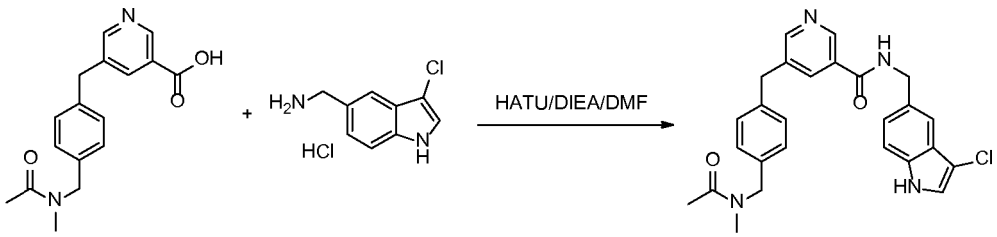


A mixture of N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide (158 mg, 0.29 mmol, 1.0 eq) in HCl/MeOH (25% w/w, 10 mL) was stirred at rt overnight. The mixture was purified directly by flash chromatography to afford N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide as a white solid (107.7 mg, 81%). LRMS ($M+H^+$) m/z calculated 462.17, found 462.4. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.08 (s, 1 H), 9.30 (t, 1 H), 8.87 (s, 1 H), 8.63 (s, 1 H), 8.06 (s, 1 H), 7.90 (s, 1 H), 7.53 (d, 1 H), 7.33 (dd, 1 H), 7.28-7.21 (m, 2 H), 7.15-7.11 (m, 2 H), 4.78 (d, 2 H), 4.49 (s, 1 H), 4.42 (s, 1 H), 4.00 (d, 2 H), 2.86 (s, 2 H), 2.75 (s, 1 H), 2.08-2.01 (m, 3 H).

Example 128: Preparation of N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide



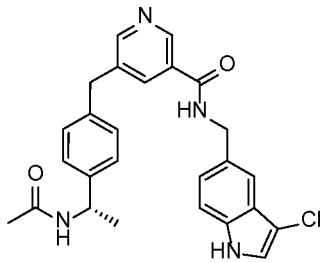
N-((3-chloro-1*H*-indol-5-yl)methyl)-5-(4-((*N*-methylacetamido)methyl)benzyl)nicotinamide



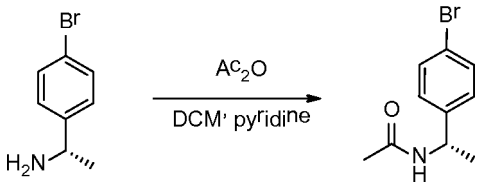
A mixture of 5-(4-((N-methylacetamido)methyl)benzyl)nicotinic acid (277 mg, crude, 0.48 mmol, 1.0 eq), (3-chloro-1H-indol-5-yl)methanamine HCl (104 mg, 0.48 mmol, 1.0 eq), HATU (274 mg, 0.72 mmol,1.5 eq) and DIEA (185 mg, 1.44 mmol, 3.0 eq) in DMF (5 mL) was stirred at rt for 2 h. The mixture was purified directly by flash chromatography to afford N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide as a white solid (86.6 mg, 39%). LRMS ($M+H^+$) m/z calculated 461.17, found 461.2. ^{1}H NMR (DMSO-d6, 400 MHz) δ 13.33 (s, 1 H), 9.21 (t, 1 H), 8.89 (s, 1 H), 8.64 (s, 1 H), 8.07 (s, 1 H), 7.50 (s, 1 H), 7.42 (s, 1 H), 7.37 (d, 1 H), 7.27 (d, 1 H), 7.22 (d, 1 H), 7.18-7.12 (m, 3 H), 4.56 (d, 2 H), 4.50 (s, 0.8H), 4.43 (s, 1.3H), 4.01 (d, 2 H), 2.86 (s, 2 H), 2.75 (s, 1 H), 2.08-2.01 (m, 3 H).

Example 129: Preparation of (S)-5-(4-(1-acetamidoethyl)benzyl)-N-((3-chloro-1H-indol-5-

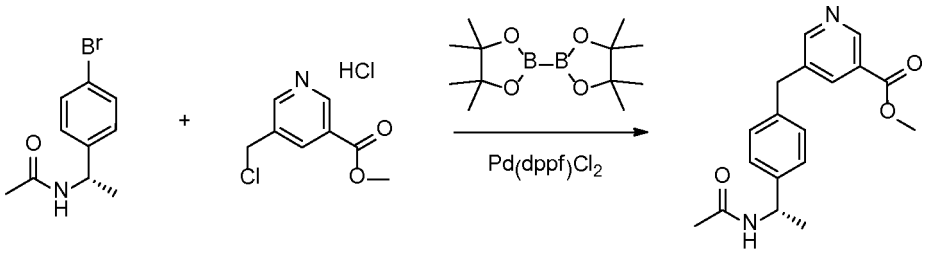
yl)methyl)nicotinamide



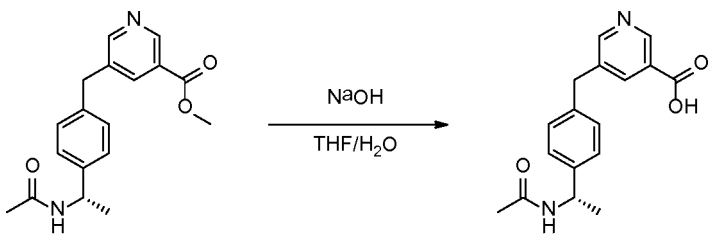
(S)-5-(4-(1-acetamidoethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



To the solution of (S)-1-(4-bromophenyl)ethanamine (2.0 g, 10.0 mmol, 1.0 eq) and pyridine (1.2 mL, 15.0 mmol, 1.5 eq) in DCM (5 mL) was added acetic anhydride (1.4 mL, 15.0 mmol, 1.5 eq) at 0 °C. The reaction was stirred at rt for 2 h, quenched with water, and the DCM layer was separated, washed twice with 2 N HCl, water, brine, dried over anhydrous sodium sulfate, and purified on silica gel column (PE/EA = 2/1) to afford (S)-N-(1-(4-bromophenyl)ethyl)acetamide as a white solid (1.8 g, 75%).

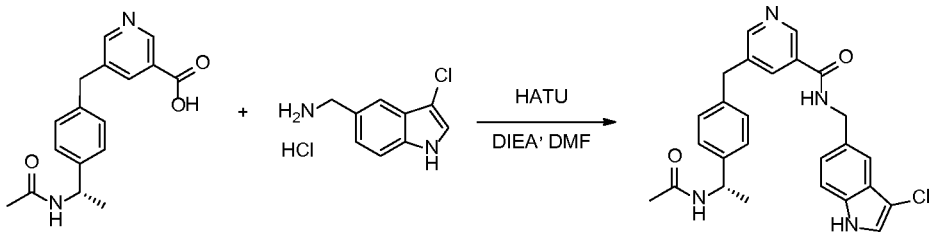


The mixture of (S)-N-(1-(4-bromophenyl)ethyl)acetamide (710 mg, 2.920 mmol, 1.3 eq), 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4',4',5',5'-tetramethyl-1,3,2-dioxaborolane (743 mg, 2.92 mmol, 1.3 eq), potassium acetate (860 mg, 8.76 mmol, 3.0 eq) and (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (105 mg, 5 mol%) in 1,4-dioxane (20 mL) was degassed and stirred at 80 °C for 6 h, cooled to rt, methyl 5-(chloromethyl)nicotinate hydrochloride (500 mg, 2.25 mmol, 1.0 eq), (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (105 mg, 5 mol%) and an aqueous sodium carbonate (1.50 g, 15.0 mmol, 5.0 eq) in water (4 mL) were added successively. The mixture was degassed again and stirred at 65 °C overnight, cooled, filtered through celite, rinsed with DCM. The DCM layer was washed with water, brine, dried over anhydrous sodium sulfate, and purified on silica gel column (PE/EA = 2/1) to afford (S)-methyl 5-(4-(1-acetamidoethyl)benzyl)nicotinate as a brown solid (580 mg, 63%).



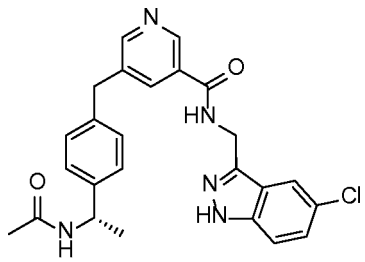
The solution of (S)-methyl 5-(4-(1-acetamidoethyl)benzyl)nicotinate (580 mg, 1.85 mmol, 1.0 eq) in THF (10 mL) was added an aqueous solution of sodium hydroxide (148 mg, 3.7 mmol, 2.0 eq) in water (4 mL). The

reaction was stirred for 1 h. The mixture was acidified with 2 N HCl to pH 2, concentrated. The residue was washed with 10% MeOH in DCM, filtered, and the filtrate was dried over anhydrous sodium sulfate and concentrated to dryness to afford (S)-5-(4-(1-acetamidoethyl)benzyl)nicotinic acid as a yellow solid (550 mg, quantitative).

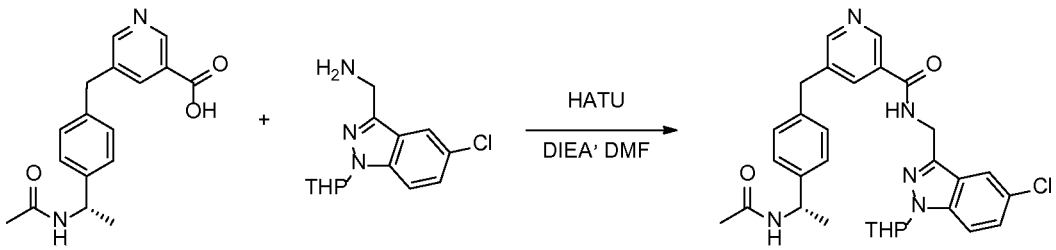


To the solution of (S)-methyl 5-(4-(1-acetamidoethyl)benzyl)nicotinate (140 mg, 0.47 mmol, 1.0 eq) in DMF (4 mL) was added HATU (232 mg, 0.61 mmol, 1.3 eq), DIEA (0.7 mL) and (3-chloro-1H-indol-5-yl)methanamine hydrochloride (110 mg, 0.5 mmol, 1.0 eq) successively. The reaction was purified via flash chromatography to afford (S)-5-(4-(1-acetamidoethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide as a yellow solid (90 mg, 41%). LRMS $(M+H)^+$ m/z calculated 461.1, found 461.1.^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.31 (s, 1 H), 9.19 (t, 1 H), 8.88 (s, 1 H), 8.63 (s, 1 H), 8.20 (d, 1 H), 8.06 (s, 1 H), 7.49 (s, 1 H), 7.42 (s, 1 H), 7.37 (d, 1 H), 7.23-7.19 (m, 4 H), 7.17 (d, 1 H), 4.86-4.81 (m, 1 H), 4.56 (d, 1 H), 3.99 (s, 1 H), 1.79 (s, 3 H), 1.29 (d, 3 H).

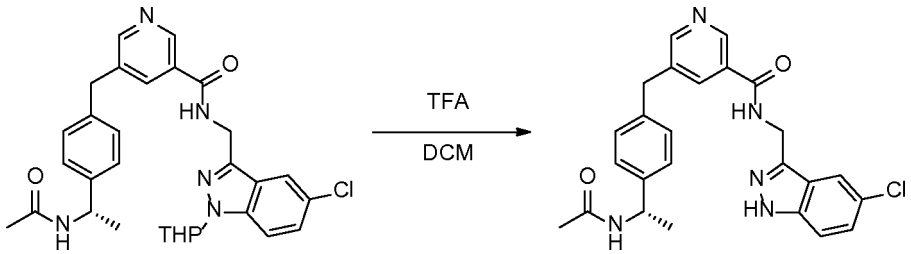
Example 130: Preparation of (S)-5-(4-(1-acetamidoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide



(S)-5-(4-(1-acetamidoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide

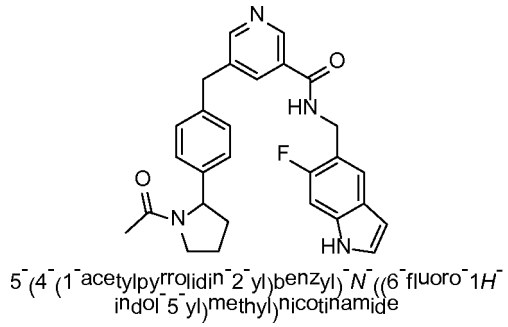


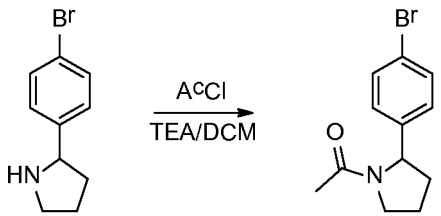
To the solution of (S)-methyl 5-(4-(1-acetamidoethyl)benzyl)nicotinate (298 mg, 1.0 mmol, 1.0 eq) in DMF (4 mL) was added HATU (495 mg, 1.3 mmol, 1.3 eq), DIEA (1.0 mL) and (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (265 mg, 1.0 mmol, 1.0 eq) successively. The reaction was stirred for 1 h, added to ice-water dropwise with stirring, and the precipitate was collected by filtration, dried to afford 5-(4-((S)-1-acetamidoethyl)benzyl)-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide as a yellow solid (400 mg, 73%).



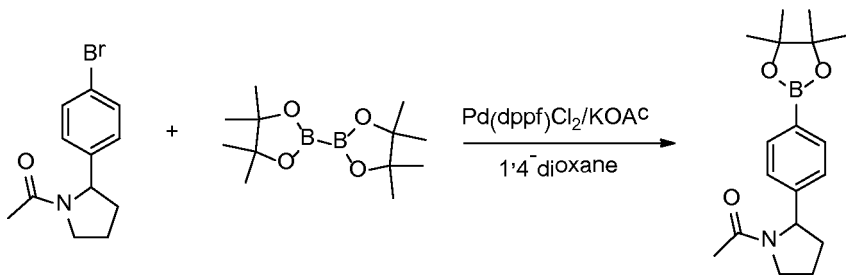
5-(4-((S)-1-acetamidoethyl)benzyl)-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide (400 mg, 0.73 mmol, 1.0 eq) was treated with trifluoroacetic aicd (2.5 mL) and DCM (2.5 mL) with stirring for 1 h and then it was concentrated. The residue was washed with saturated aqueous sodium bicarbonate carefully, and the solid was collected and purified via flash chromatography to afford (S)-5-(4-(1-acetamidoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide as a yellow solid (150 mg, 41%). LRMS $(M+H)^+$ m/z calculated 461.1, found 461.1.^{1}H NMR (DMSO-d6, 400 MHz) δ 11.31 (s, 1 H), 9.19 (t, 1 H), 8.88 (s, 1 H), 8.63 (s, 1 H), 8.20 (d, 1 H), 8.06 (s, 1 H), 7.49 (s, 1 H), 7.42 (s, 1 H), 7.37 (d, 1 H), 7.23-7.19 (m, 4 H), 7.17 (d, 1 H), 4.86-4.81 (m, 1 H), 4.56 (d, 1 H), 3.99 (s, 1 H), 1.79 (s, 3 H), 1.29 (d, 3 H).

Example 131: Preparation of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((6-fluoro-1H-indol-5-yl)methyl)nicotinamide

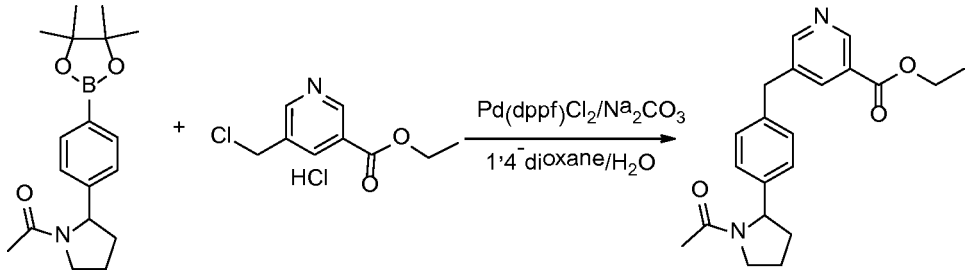




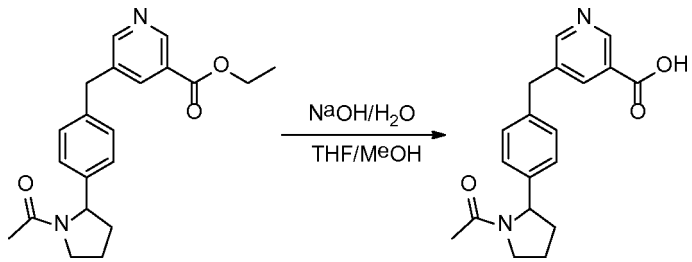
To the solution of 2-(4-bromophenyl)pyrrolidine (914 mg, 4.04 mmol, 1.0 eq) and TEA (2.5 mL, 18 mmol, 4 eq) in DCM (15 mL) was added AcCl (0.38 mL, 5.35 mmol, 1.3 eq). The mixture was stirred at rt overnight and washed with water (20 mL), dried over anhydrous Na_2SO_4 and concentrated to afford 1-(2-(4-bromophenyl)pyrrolidin-1-yl)ethanone as a yellow oil (1.14 g crude, quant).



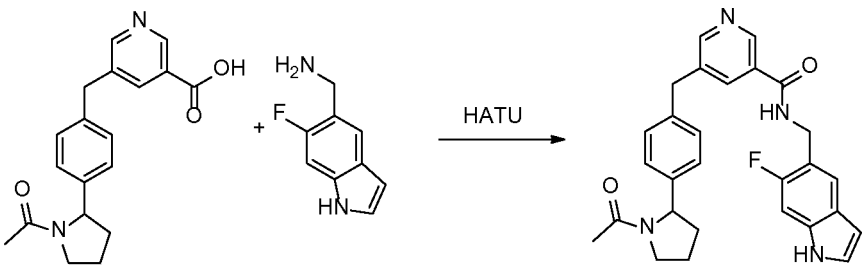
A mixture of 1-(2-(4-bromophenyl)pyrrolidin-1-yl)ethanone (1.14 g, 4 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.07 g, 4.2 mmol, 1.05 eq), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (327 mg, 0.4 mmol, 0.1 eq), KOAc (1.18 g, 12 mmol, 3 eq) in 1,4-dioxane (20 mL) under N_2 was stirred at 85 °C overnight. The mixture was and concentrated and the residue was purified on silica gel column (EA/PE = 2/3, v/v) to afford 1-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)ethanone as a yellow oil (1.39 g crude, quant).



The reaction mixture of 1-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)ethanone (1.39 g, 4 mmol, 1eq), ethyl 5-(chloromethyl)nicotinate hydrochloride (932 mg, 4.2 mmol, 1.05 eq), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (327 mg, 0.4 mmol, 0.1 eq) and Na_2CO_3 (2.12 g, 20 mmol, 5 eq) in 1,4-dioxane/H_2O (15 mL/1.5 mL) was degassed with N_2 and stirred at 80 °C overnight .The mixture was filtered and concentrated. The residue was purified on silica gel column (EA/PE = 1/1-1/0, v/v) to afford ethyl 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)nicotinate as a yellow oil (973 mg, 72%).



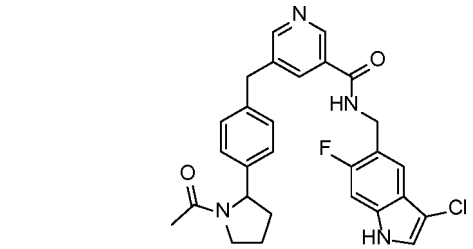
To a solution of ethyl 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)nicotinate (973 mg, 2.88 mmol, 1.0 eq) in MeOH (5 mL) and THF (10 mL) was added a solution of LiOH (400 mg, 9.52 mmol, 3.3 eq) in water (5 mL). The mixture was stirred at rt for 3 h. The organic solvents were evaporated and the residue was acidified by HCl to pH 3. The mixture was concentrated to afford 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)nicotinic acid as a yellow solid (1.9 g, mixed with inorganic salt).



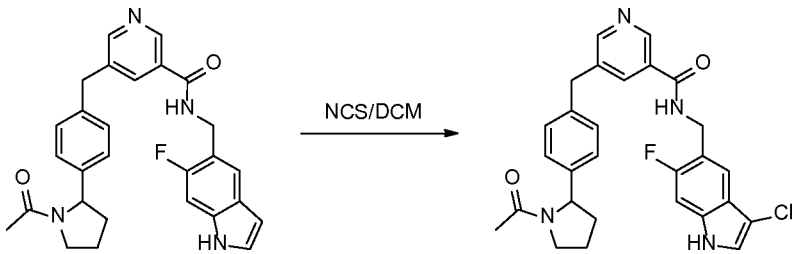
A mixture of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)nicotinic acid (162 mg, 0.5 mmol, 1.0 eq), (6-fluoro-1H-indol-5-yl)methanamine (82 mg, 0.5 mmol, 1.0 eq), HATU (228 mg, 0.6 mmol, 1.2 eq) and DIPEA (0.8 mL) in DMF (3 mL) was stirred at rt overnight. The mixture was purified via prep-MPLC to afford 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((6-fluoro-1H-indol-5-yl)methyl)nicotinamide as a white solid (136 mg,

57.8%). LRMS (M+H$^+$) m/z calculated 471.2, found 471.2. ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 11.10 (s, 1 H), 9.12 (t, 1 H), 8.90 (dd, 1 H), 8.64 (dd, 1 H), 8.10 (d, 1 H), 7.50 (d, 1 H), 7.31 (t, 1 H), 7.25 (d, 1 H), 7.18 (d, 1 H), 7.15 (d, 1 H), 7.11 (d, 1 H), 7.06 (d, 1 H), 6.40 (s, 1 H), 4.97 (t, 1 H) , 4.55 (d, 2 H), 4.00 (d, 2 H), 3.73-3.45 (m, 2 H), 2.33-2.13 (m, 1 H), 2.00 (s, 1.5 H), 1.86-1.67 (m, 3 H), 1.66 (s, 1.5 H).

Example 132: Preparation of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide

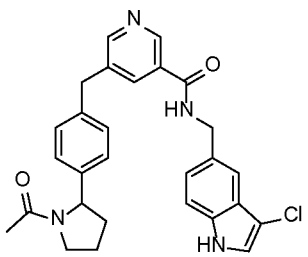


5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide

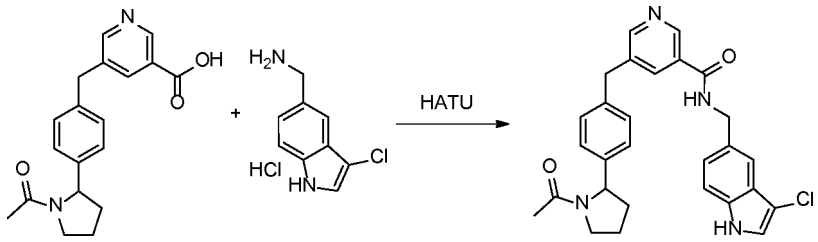


To the solution of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((6-fluoro-1H-indol-5-yl)methyl)nicotinamide (95 mg, 0.2 mmol, 1.0 eq) in DCM (5 mL) was added NCS (56 mg, 0.42 mmol, 2.1 eq). The mixture was stirred at rt for 2 h and concentrated. The residue was purified via prep-MPLC to afford5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide as a white solid (40 mg, 39.2%). LRMS (M+H$^+$) m/z calculated 505.2, found 505.2. ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 11.39 (s, 1 H), 9.16 (t, 1 H), 8.89 (dd, 1 H), 8.64 (dd, 1 H), 8.09 (d, 1 H), 7.50 (d, 1 H), 7.45 (d, 1 H), 7.25 (d, 1 H), 7.22 (d, 1 H), 7.17 (d, 1 H), 7.11 (d, 1 H), 7.06 (d, 1 H), 4.97 (t, 1 H) , 4.59 (d, 2 H), 4.00 (d, 2 H), 3.73-3.45 (m, 2 H), 2.33-2.13 (m, 1 H), 2.00 (s, 1.5 H), 1.87-1.70 (m, 3 H), 1.65 (s, 1.5 H).

Example 133: Preparation of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide

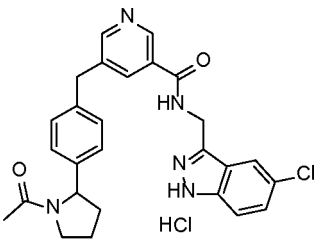


5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide

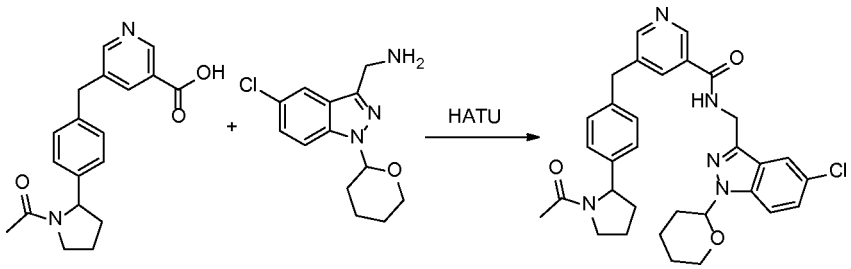


A mixture of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)nicotinic acid (162 mg, 0.5 mmol, 1.0 eq), (3-chloro-1H-indol-5-yl)methanamine hydrochloride (117 mg, 0.5 mmol, 1.0 eq), HATU (228 mg, 0.6 mmol, 1.2 eq) and DIPEA (1 mL) in DMF (3 mL) was stirred at rt overnight. The mixture was purified via prep-MPLC to afford 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide as a white solid (120 mg, 49.4%). LRMS ($M+H^+$) m/z calculated 487.2, found 487.5. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.32 (s, 1 H), 9.20 (t, 1 H), 8.89 (dd, 1 H), 8.63 (dd, 1 H), 8.09-8.08 (m, 1 H), 7.49 (d, 1 H), 7.43 (s, 1 H), 7.37 (d, 1 H), 7.25 (d, 1 H), 7.17 (d, 2 H), 7.11 (d, 1 H), 7.06 (d, 1 H), 4.97 (t, 1 H) , 4.56 (d, 2 H), 4.00 (d, 2 H), 3.73-3.45 (m, 2 H), 2.37-2.13 (m, 1 H), 2.00 (s, 1.5 H), 1.87-1.66 (m, 3 H), 1.65 (s, 1.5 H).

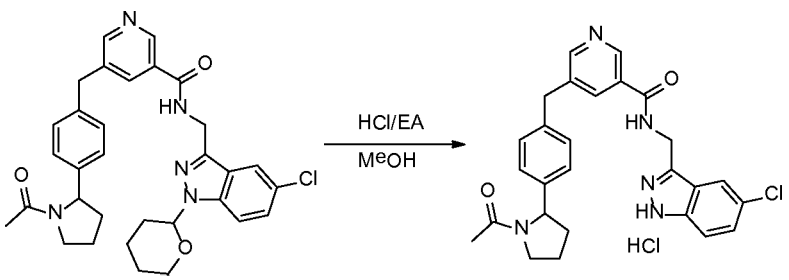
Example 134: Preparation of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide



5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide hydrochloride

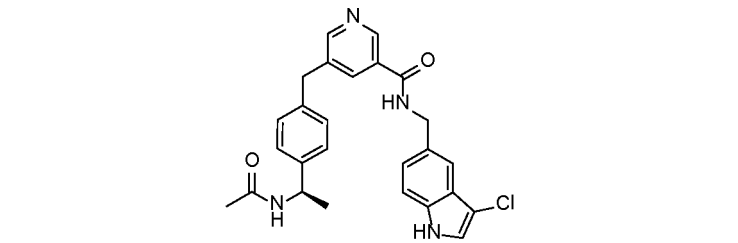


A mixture of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)nicotinic acid (162 mg, 0.5 mmol, 1.0 eq), (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (133 mg, 0.5 mmol, 1.0 eq), HATU (228 mg, 0.6 mmol, 1.2 eq) and DIPEA (0.8 mL) in DMF (3 mL) was stirred at rt overnight. The mixture was purified via prep-MPLC to afford 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide as a yellow solid (216 mg, 75.7%).

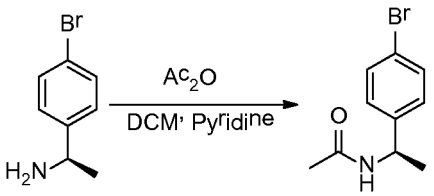


A solution of 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide (100 mg, 0.175 mmol, 1 eq) in MeOH (0.5 mL) and HCl/EA (5 N, 2 mL) was stirred at rt overnight, then filtered. The solid was collected to afford 5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide hydrochloride as a yellow solid (47 mg, 51.2%).LRMS ($M+H^+$) m/z calculated 488.2, found 488.1. ^1H NMR (CD_3OD, 400 MHz) δ 9.18 (d, 1 H), 8.94 (s, 1 H), 8.90 (d, 1 H), 7.93 (s, 1 H), 7.53 (d, 1 H), 7.40 (dd, 1 H), 7.37 (d, 1 H), 7.29 (d, 1 H), 7.23 (d, 1 H), 7.19 (d, 1 H), 5.16 - 5.12 (m, 1 H), 4.98 (s, 2 H) , 4.30 (d, 2 H), 3.89-3.68 (m, 2 H), 2.50-2.33 (m, 1 H), 2.21 (s, 1.5 H), 2.04-1.85 (m, 3 H), 1.86 (s, 1.5 H).

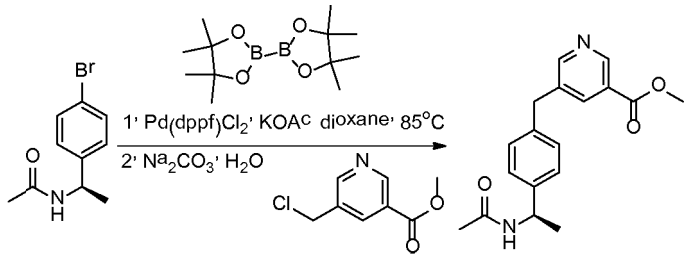
Example 135: Preparation of (R)-5-(4-(1-acetamidoethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



(*R*)-5-(4-(1-acetamidoethyl)benzyl)-*N*-((3-chloro-1*H*-indol-5-yl)methyl)nicotinamide

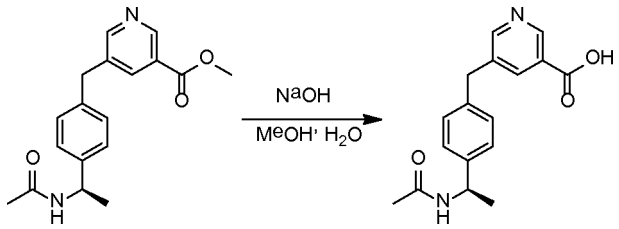


To a solution of (R)-1-(4-bromophenyl)ethanamine (2.0 g, 10 mmol, 1.0 eq) in DCM (20 mL) were added pyridine (1.19 g, 15 mmol, 1.5 eq) and Ac_2O (1.53 g, 15 mmol, 1.5 eq) at 0 °C under N_2. The suspension was stirred at rt overnight. The reaction mixture was added 1 N HCl (20 mL), extracted with EA (20 mL ×3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified via flash chromatography to afford (R)-N-(1-(4-bromophenyl)ethyl)acetamide as a white solid (2.0 g, 83%).

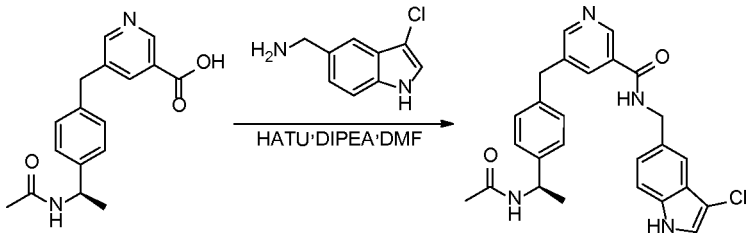


To a solution of (R)-N-(1-(4-bromophenyl)ethyl)acetamide (653 mg, 2.69 mmol, 1.0 eq) in 1,4-dioxane (30 mL) were added KOAc (794 mg, 8.1 mmol, 3.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (686 mg, 2.69 mmol, 1.0 eq) and $Pd(dppf)Cl_2$ (99 mg, 0.14 mmol, 0.05 eq). The mixture was heated at 85 °C overnight under N_2, and then the mixture was cooled to rt. To the mixture were added methyl 5-(chloromethyl)nicotinate (500 mg, 2.69 mmol, 1.0 eq), $Pd(dppf)Cl_2$ (99 mg, 0.14 mmol, 0.05 eq) and Na_2CO_3 (859 mg, 8.1 mmol, 3.0 eq) in water (6 mL). The mixture was heated to 80 °C overnight under N_2. The

mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (10 mL) and extracted with EA (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column (DCM/MeOH = 200/1 to 50/1) to afford (R)-methyl 5-(4-(1-acetamidoethyl)benzyl)nicotinate as a yellow solid (320 mg, 38%).

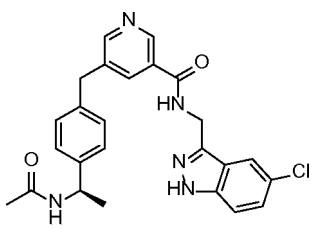


To a solution of (R)-methyl 5-(4-(1-acetamidoethyl)benzyl)nicotinate (320 mg, 1.03 mmol, 1.0 eq) in MeOH (4 mL) and H_2O (4 mL) was added NaOH (124 mg, 3.09 mmol, 3.0 eq). The mixture was heated at 60 °C for 30 min. The mixture was concentrated to remove MeOH, then diluted with ice-water (5 mL) and acidified with 1 N HCl to pH 2-3. The mixture was concentrated to dryness under reduced pressure. The residue was re-dissolved in MeOH (10 mL) and filtered. The filtrate was concentrated under reduced pressure to afford (R)-5-(4-(1-acetamidoethyl)benzyl)nicotinic acid as a yellow solid (500 mg crude, quant).

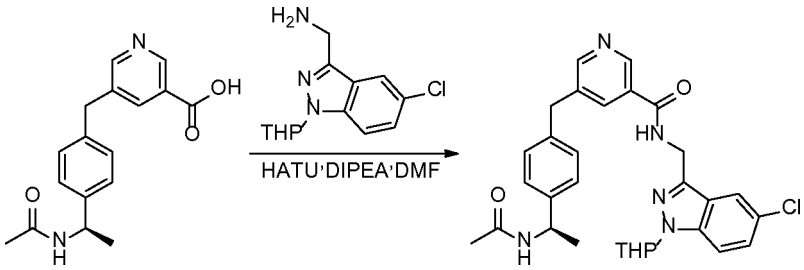


To a solution of (R)-5-(4-(1-acetamidoethyl)benzyl)nicotinic acid (250 mg crude, 0.52 mmol, 1.0 eq) in DMF (3 mL) were added DIPEA (335 mg, 2.6 mmol, 5.0 eq) and HATU (237 mg, 0.62 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (3-chloro-1H-indol-5-yl)methanamine (113 mg, 0.52 mmol, 1.0 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was purified via flash chromatography to afford (R)-5-(4-(1-acetamidoethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide as a white solid (122 mg, 51%). LRMS ($M+H^+$) m/z caculated 461.1, found 461.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.32 (brs, 1 H), 9.20 (t, 1 H), 8.88 (d, 1 H), 8.63 (d, 1 H), 8.20 (d, 1 H), 8.06 (s, 1 H), 7.49 (d, 1 H), 7.42 (s, 1 H), 7.37 (d, 1 H), 7.30-7.20 (m, 4 H), 7.15 (d, 1 H), 4.90-4.80 (m, 1 H), 4.56 (d, 2 H), 3.99 (s, 2 H), 1.79 (s, 3 H), 1.28 (d, 3 H).

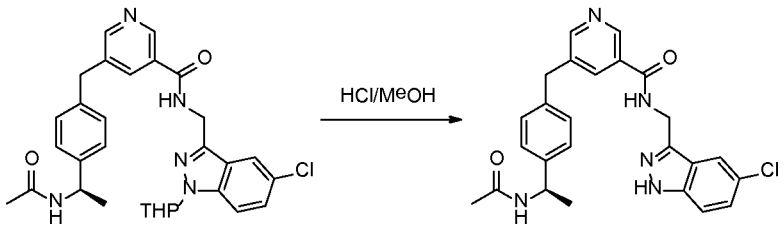
Example 136: Preparation of (R)-5-(4-(1-acetamidoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide



(*R*)-5-(4-(1-acetamidoethyl)benzyl)-*N*-((5-chloro-1*H*-indazol-3-yl)methyl)nicotinamide

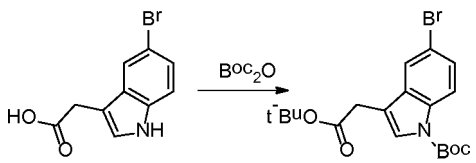


To a solution of (R)-5-(4-(1-acetamidoethyl)benzyl)nicotinic acid (250 mg crude, 0.52 mmol, 1.0 eq) in DMF (3 mL) were added DIPEA (335 mg, 2.6 mmol, 5.0 eq) and HATU (237 mg, 0.62 mmol, 1.2 eq) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, (5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methanamine (138 mg, 0.52 mmol, 1.0 eq) was then added and the mixture was stirred at rt overnight under N_2. The mixture was purified via flash chromatography to afford 5-(4-((R)-1-acetamidoethyl)benzyl)-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide as a white solid (220 mg, 77%).

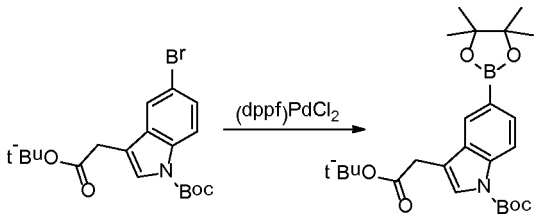


To a solution of 5-(4-((R)-1-acetamidoethyl)benzyl)-N-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)methyl)nicotinamide (220 mg, 0.4 mmol, 1.0 eq) in MeOH (2 mL) was added HCl/MeOH (2 mL) at 0 °C. The mixture was stirred at rt for 2 h. The mixture was concentrated to dryness under reduced pressure. The residue was mixed with water (5 mL), neutralized with saturated $NaHCO_3$ (5 mL) and concentrated. The residue was purified via flash chromatography to afford (R)-5-(4-(1-acetamidoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide as a white solid (102 mg, 55%). LRMS ($M+H^+$) m/z caculated 462.1, found 462.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 13.08 (brs, 1 H), 9.30 (t, 1 H), 8.86 (d, 1 H), 8.63 (d, 1 H), 8.21 (d, 1 H), 8.06 (s, 1 H), 7.90 (d, 1 H), 7.53 (d, 1 H), 7.34 (dd, 1 H), 7.30-7.20 (m, 4 H), 4.90-4.80 (m, 1 H), 4.78 (d, 2 H), 3.98 (s, 2 H), 1.80 (s, 3 H), 1.28 (d, 3 H).

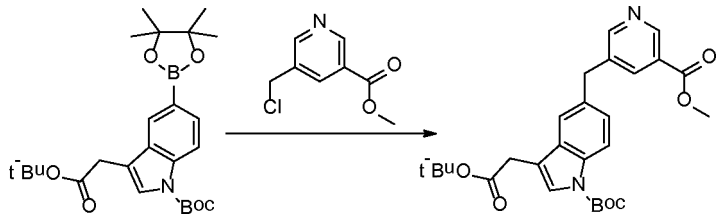
Example 137: Preparation of 2-(5-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridine-3-yl) methyl)-1H-indol-3-yl)acetic acid



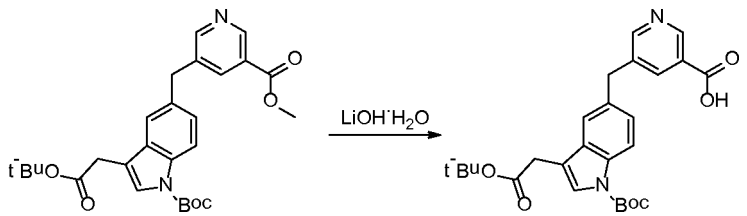
To a solution of (5-bromo-1H-indol-3-yl)-acetic acid (2.8 g, 11.0 mmol, 1 eq) in *t*-BuOH (20 mL) /THF (60 mL) was added Boc_2O (12.0 g, 55.0 mmol, 5 eq) and DMAP (134 mg, 1.1 mmol, 0.1 eq). The mixture was stirred at 80 °C overnight. The reaction mixture was concentrated in vacuo. And the residue was purified by chromatography on a silica gel column (EA/PE = 1/ 100) to give 5-bromo-3-*tert*-butoxycarbonylmethyl-indole-1-carboxylic acid *tert*-butyl ester (1.29 g, 29%) as a yellow solid.



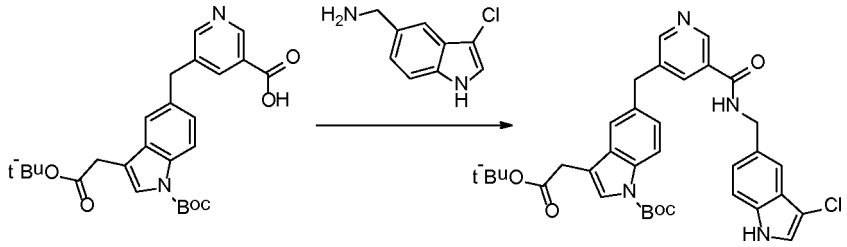
To a solution of 5-bromo-3-tert-butoxycarbonylmethyl-indole-1-carboxylic acid *tert*-butyl ester (1.20 g, 2.93 mmol, 1 eq) and $B_2(Pin)_2$ (895 mg, 3.52 mmol, 1.2 eq) in dioxane (25 mL) was added KOAc (862 mg, 8.79 mmol, 3 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (120 mg, 0.15 mmol, 0.05 eq). The mixture was stirred at 95 °C for 2 h and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column to give compound 3-*tert*-butoxycarbonylmethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid *tert*-butyl ester (1.0 g, 75%) as a white solid.



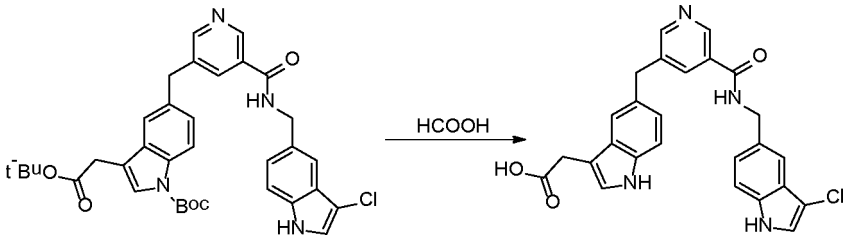
To a solution of 3-*tert*-butoxycarbonylmethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid *tert*-butyl ester (1.14 g, 2.5 mmol, 1 eq) and 5-chloromethyl-nicotinic acid methyl ester (555 mg, 2.5 mmol, 1 eq) in dioxane (25 mL) and water (5 mL) was added K_2CO_3 (1.38 g, 10.0 mmol, 4 eq), and $Pd(PPh_3)_4$ (150 mg, 0.125 mmol, 0.05 eq). The mixture was stirred at 95 °C for 1 h under nitrogen and then it was diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (EA/ PE = 1/5) to give 3-*tert*-butoxycarbonylmethyl-5-(5-methoxycarbonyl-pyridin-3-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester (1.02 g, 85%) as a colorless oil.



To a solution of 3-*tert*-butoxycarbonylmethyl-5-(5-methoxycarbonyl-pyridin-3-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester (1.0 g, 2.08 mmol, 1 eq) in THF (7 mL), MeOH (7 mL) and H_2O (7 mL) was added $LiOH.H_2O$ (96 mg, 2.29 mmol, 1.1 eq). The mixture was stirred at rt for 2 h and was acidified to pH 5~6 with 1 N HCl solution. The mixture was extracted with EA and the combined organic layer was dried and concentrated. The residue (945 mg, quant) as a white solid was directly used without further purification.

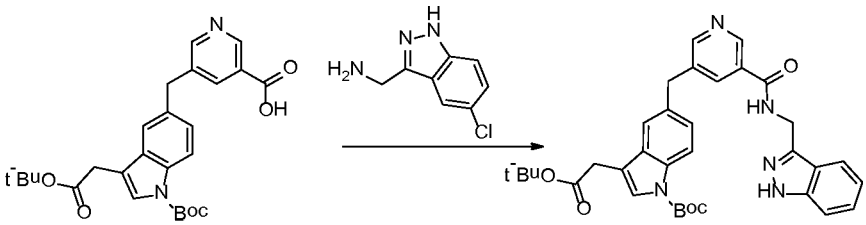


To a solution of 3-*tert*-butoxycarbonylmethyl-5-(5-carboxy-pyridin-3-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester (200 mg, 0.43 mmol, 1 eq) and c-(3-chloro-1H-indol-5-yl)-methylamine (102 mg, 0.473 mmol, 1.1 eq) in DCM (5 mL) was added HOBT (88 mg, 0.645 mmol, 1.5 eq), EDCI (124 mg, 0.645 mmol, 1.5 eq) and Et_3N (0.18 mL, 1.29 mmol, 3 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (EA/PE = 1/ 1) to give 3-*tert*-butoxycarbonylmethyl-5-{5-[(3-chloro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-indole-1-carboxylic acid *tert*-butyl ester (200 mg, 74%) as a white solid.



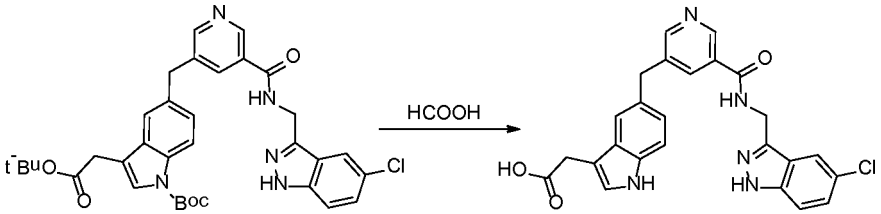
3-*tert*-Butoxycarbonylmethyl-5-{5-[(3-chloro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-indole-1-carboxylic acid *tert*-butyl ester (80 mg, 0.127 mmol) was treated with HCOOH (4 mL) and the mixture was stirred at rt for 30 h. The mixture was concentrated in vacuo and the residue was purified by prep-HPLC to give 2-(5-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-1H-indol-3-yl)acetic acid (19 mg, 32%) as a white solid. LRMS ($M+H^+$) m/z calculated 473.1, found 473.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.77 (s, 1 H), 8.51 (s, 1 H), 8.10 (s, 1 H), 7.47 (s, 1 H), 7.40 (s, 1 H), 7.30 (d, 1 H), 7.25 (d, 1 H), 7.20 (s, 1 H), 7.15 (dd, 1 H), 7.13 (s, 1 H), 6.91 (dd, 1 H), 4.60 (s, 2 H), 4.07 (s, 2 H), 3.68 (s, 2 H).

Example 138: Preparation of 2-(5-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl) pyridine-3-yl)methyl)-1 H-indol-3-yl)acetic acid



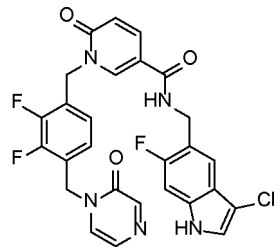
To a solution of 3-*tert*-butoxycarbonylmethyl-5-(5-carboxy-pyridin-3-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester (230 mg, 0.49 mmol, 1 eq) and C-(5-chloro-1H-indazol-3-yl)-methylamine (108 mg, 0.59 mmol, 1.2 eq) in DCM (5 mL) was added HOBT (100 mg, 0.74 mmol, 1.5 eq), EDCI (142 mg, 0.74 mmol, 1.5 eq) and Et_3N (0.21 mL, 1.48 mmol, 3 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers

were dried and concentrated. The residue was purified by chromatography on a silica gel column (EA/PE = 1/1) to give 3-*tert*-butoxycarbonylmethyl-5-{5-[(5-chloro-1H-indazol-3-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-indole-1-carboxylic acid *tert*-butyl ester (210 mg, 67%) as a white solid.



3-*tert*-Butoxycarbonylmethyl-5-{5-[(5-chloro-1H-indazol-3-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-indole-1-carboxylic acid *tert*-butyl ester (80 mg, 0.128 mmol) was treated with HCOOH (4 mL) and the mixture was stirred at rt for 30 h. The mixture was concentrated in vacuo and the residue was purified by prep-HPLC to give 2-(5-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-1 H-indol-3-yl)acetic acid (25 mg, 42%) as an off-white solid. LRMS ($M+H^+$) m/z calculated 474.1, found 474.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.82 (s, 1 H), 8.58 (s, 1 H), 8.13 (s, 1 H), 7.88 (d, 1 H), 7.49 (d, 1 H), 7.46 (s, 1 H), 7.35 (dd, 1 H), 7.31 (d, 1 H), 7.18 (s, 1 H), 6.98 (dd, 1 H), 4.90 (s, 2 H), 4.16 (s, 2 H), 3.73 (s, 2 H).

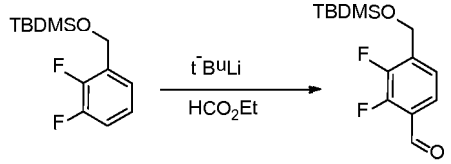
Example 139: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(2,3-difluoro-4 -((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2*H*)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

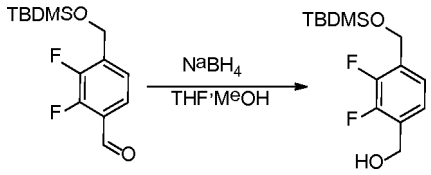


To a solution of (2,3-difluoro-phenyl)-methanol (50 g, 0.35 mol, 1.0 eq) and imidazole (70.9 g, 1.05 mol, 3.0 eq) in dry THF (1 L) was added TBDMSCl (62.7 g, 0.42 mol, 1.2 eq) at ice-bath. After stirring at rt for 3 h, the mixture was extracted with EA, and washed with water and 0.5 N HCl. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product (90 g), which was directly used in next step.

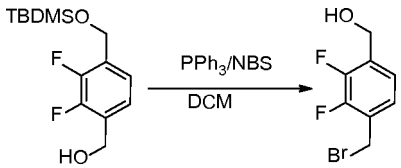


A 1.3 N solution of *t*-BuLi in THF (292 mL, 0.38 mol, 1.1 eq) was added to a solution of *tert*-butyl-(2,3-difluoro-benzyloxy)-dimethyl-silane (90 g, 0.35 mol, 1.0 eq) in dry THF (800 mL) at -78 °C under argon atmosphere. After stirring for 2 h, DMF (28 g, 0.38 mol, 1.1 eq) was added. The mixture was stirred at room temperature overnight and was quenched with saturated aqueous NaCl and extracted with EA. The organic

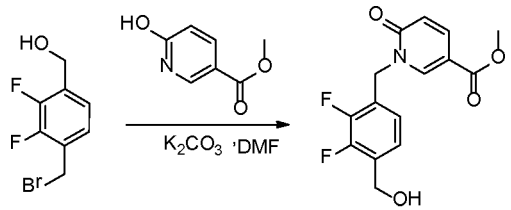
layer was dried over $MgSO_4$ and concentrated to give 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-benzaldehyde (93 g) as a colorless oil.



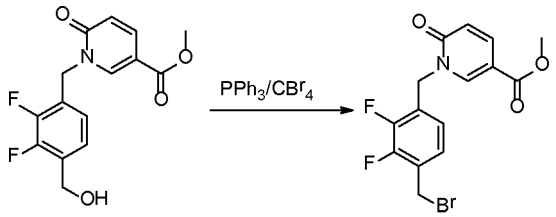
To a solution of 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-benzaldehyde (93 g, 0.32 mol, 1.0 eq) in THF (800 mL) was added $NaBH_4$ (8.6 g, 0.22 mol, 0.7 eq) at ice-bath,. And then methanol was added dropwise until LRMS showed the SM was consumed. The reaction mixture was quenched with saturated aqueous NaCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated give the crude product which was subjected to silica gel chromatography (PE/ EA = 20/ 1 -10/ 1) to afford [4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-phenyl]-methanol (42 g, 45%) as a yellow oil.



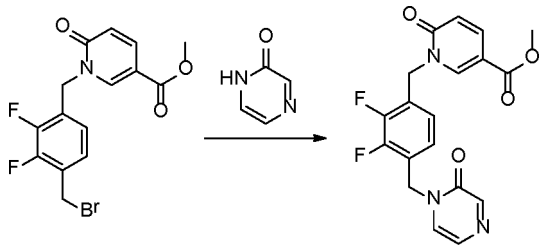
To a solution of [4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-phenyl]-methanol (10 g, 0.03 mol, 1.0 eq) in DCM (200 mL) was added PPh_3 (10.4 g, 0.04 mol, 1.15 eq) and NBS (7.1 g, 0.04 mol, 1.15 eq). The mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous NaCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to give the crude product which was subject to silica gel chromatography (DCM/ MeOH = 300/ 1 -200/1) to afford (4-bromomethyl-2,3-difluoro-phenyl)-methanol (4.4 g, 53%) as a yellow solid.



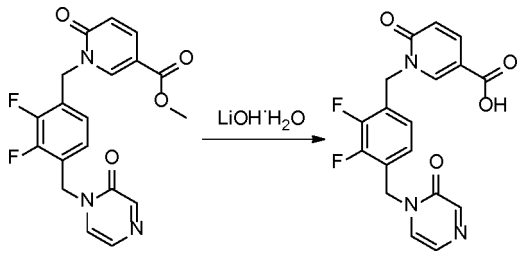
To a solution of (4-bromomethyl-2,3-difluoro-phenyl)-methanol (4.4 g, 0.02 mol, 1.0 eq) in DMF (100 mL) was added 6-hydroxy-nicotinic acid methyl ester (2.84 g, 0.02 mmol, 1.0 eq) and K_2CO_3 (8.28 g, 0.06 mmol, 3.0 eq). The reaction mixture was stirred overnight at room temperature, and was quenched with saturated aqueous NaCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (DCM/ MeOH = 200/ 1) to afford 1-(2,3-difluoro-4-hydroxymethyl-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (4 g, 70%) as a yellow solid.



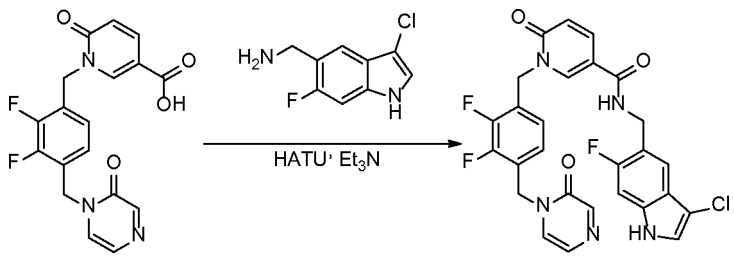
To a solution of 1-(2,3-difluoro-4-hydroxymethyl-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (2 g, 6.47 mmol, 1.0 eq) in DCM (30 mL) was added PPh_3 (1.95 g, 7.44 mmol, 1.15 eq) and CBr_4 (2.47 g, 7.44 mmol, 1.15 eq). The mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous NaCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to give the crude product which was subject to silica gel chromatography (DCM/ MeOH = 300/ 1-200/ 1) to afford 1-(4-bromomethyl-2,3-difluoro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (2.1 g, 87%) as a yellow solid.



To a solution of 1-(4-bromomethyl-2,3-difluoro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (2.1 g, 5.66 mmol, 1.0 eq) in DMF (30 mL) was added pyrazin-2-ol (543 mg, 5.66 mmol, 1.0 eq) and K_2CO_3 (2.34 g, 17 mmol, 3.0 eq). The reaction mixture was stirred overnight at room temperature, and was quenched with saturated aqueous NaCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (DCM/MeOH = 20/1) to afford 1-[2,3-difluoro-4-(2-oxo-2H-pyrazin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (850 mg, 40%) as a yellow solid.



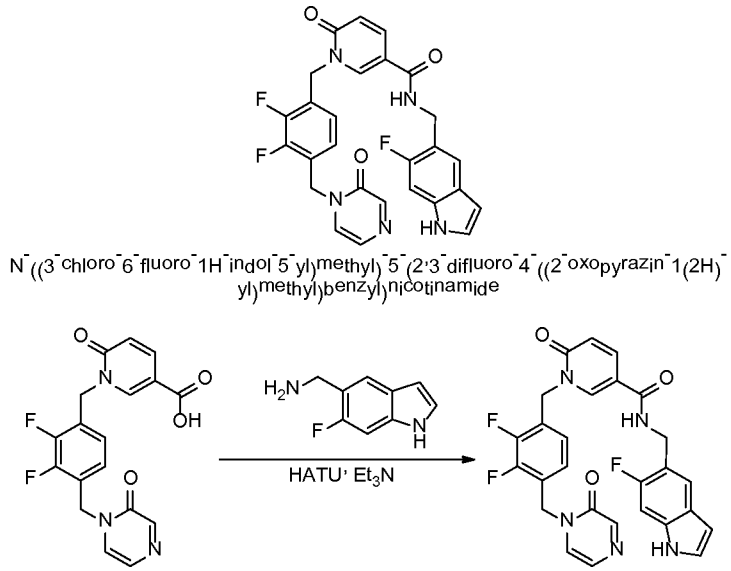
To a solution of 1-[2,3-difluoro-4-(2-oxo-2H-pyrazin-1-ylmethyl)-benzyl]-6-oxo-1,6- dihydro-pyridine-3-carboxylic acid methyl ester (840 mg, 2.16 mmol, 1.0 eq) in THF (18 mL)/ H_2O (2 mL) was added $LiOH.H_2O$ (100 mg, 2.38 mmol, 1.1 eq). The mixture was stirred at 40 °C for 30 min and was acidified to pH 5~6 with 1 N HCl solution. The mixture was concentrated in vacuo and the residue (800 mg, 99%) as a white solid was directly used without further purification.



To a solution of 1-[2,3-difluoro-4-(2-oxo-2H-pyrazin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (80 mg, 0.214 mmol, 1.0 eq) and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (50 mg, 0.214 mmol, 1.0 eq) in DCM (4 mL) was added HATU (98 mg, 0.257 mmol, 1.2 eq) and Et_3N (0.12 mL,

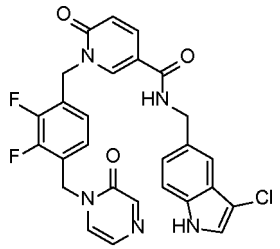
0.856 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 10/ 1) to give N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (62 mg, 52%) as a white solid. LRMS ($M+H^+$) m/z calculated 554.1, found 554.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.42 (d, 1 H), 8.07 (d, 1 H), 8.00 (dd, 1 H), 7.62 (d, 1 H), 7.52 (d, 1 H), 7.42 (d, 1 H), 7.27 (s, 1 H), 7.14 (d, 1 H), 7.15-7.06 (m, 2 H), 6.57 (d, 1 H), 5.30 (s, 2 H), 5.22 (s, 2 H), 4.69 (s, 2 H).

Example 140: Preparation of 1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-N-((6-fluoro-1 H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

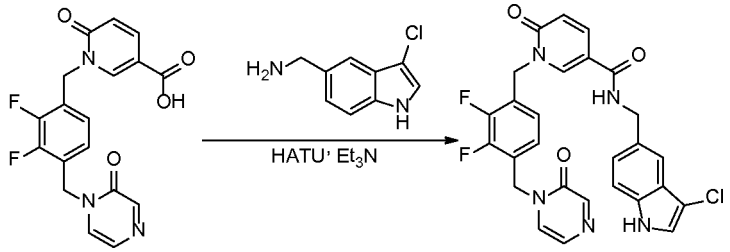


To a solution of 1-[2,3-difluoro-4-(2-oxo-2H-pyrazin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro -pyridine-3-carboxylic acid (80 mg, 0.214 mmol, 1.0 eq) and C-(6-fluoro-1 H-indol-5-yl)-methylamine (50 mg, 0.214 mmol, 1.0 eq) in DCM (4 mL) was added HATU (98 mg, 0.257 mmol, 1.2 eq) and Et_3N (0.12 mL, 0.856 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/MeOH = 10/1) to give 1-(2,3-difluoro-4-((2-oxopyrazin-1(2 H)-yl)methyl)benzyl)-N-((6-fluoro-1 H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (25 mg, 23%) as a white solid. LRMS ($M+H^+$) m/z calculated 520.1.1, found 520.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.40 (d, 1 H), 8.07 (d, 1 H), 8.00 (dd, 1 H), 7.62 (d, 1 H), 7.54 (d, 1 H), 7.41 (d, 1 H), 7.23 (d, 1 H), 7.16-7.06 (m, 3 H), 6.56 (d, 1 H), 6.43 (d, 1 H), 5.30 (s, 2 H), 5.22 (s, 2 H), 4.66 (s, 2 H).

Example 141: Preparation of N-((3-chloro-1H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2 H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

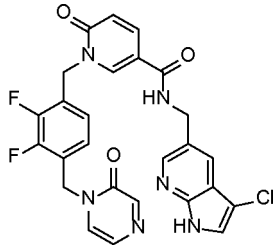


N-((3-chloro-1H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

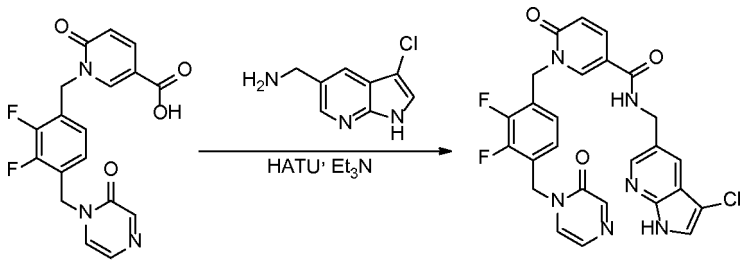


To a solution of 1-[2,3-difluoro-4-(2-oxo-2H-pyrazin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (100 mg, 0.268 mmol, 1.0 eq) and C-(3-chloro-1 H-indol-5-yl)-methylamine (70 mg, 0.322 mmol, 1.2 eq) in DCM (4 mL) was added HATU (123 mg, 0.322 mmol, 1.2 eq) and Et_3N (0.11 mL, 0.804 mmol, 3 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 20/ 1) to give N-((3-chloro-1 H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (60 mg, 42%) as an off-white solid. LRMS ($M+H^+$) m/z calculated 536.1, found 536.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.36 (d, 1 H), 8.02 (s, 1 H), 7.95 (dd, 1 H), 7.57 (d, 1 H), 7.48 (s, 1 H), 7.37 (d, 1 H), 7.32 (d, 1 H), 7.22 (s, 1 H), 7.17 (d, 1 H), 7.12-7.02 (m, 2 H), 6.52 (d, 1 H), 5.26 (s, 2 H), 5.18 (s, 2 H), 4.61 (s, 2 H).

Example 142: Preparation of N-((3-chloro-1 H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-1-(2,3-difluoro- 4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

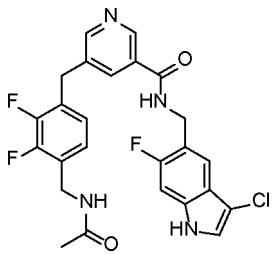


N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

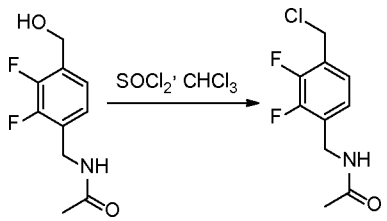


To a solution of 1-[2,3-difluoro-4-(2-oxo-2H-pyrazin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (100 mg, 0.268 mmol, 1.0 eq) and C-(3-chloro-1 H-pyrrolo[2,3-b]pyridin-5-yl)-methylamine (72 mg, 0.322 mmol, 1.2 eq) in DCM (4 mL) was added HATU (123 mg, 0.322 mmol, 1.2 eq) and Et_3N (0.11 mL, 0.804 mmol, 3 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/MeOH = 10/ 1) to give N-((3-chloro-1 H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (48 mg, 34%) as an off-white solid. LRMS ($M+H^+$) m/z calculated 537.1, found 537.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.41 (d, 1 H), 8.32 (d, 1 H), 8.06 (d, 1 H), 8.00 (d, 1 H), 7.97 (dd, 1 H), 7.61 (d, 1 H), 7.44 (s, 1 H), 7.41 (d, 1 H), 7.16-7.06 (m, 2 H), 6.56 (d, 1 H), 5.30 (s, 2 H), 5.22 (s, 2 H), 4.68 (s, 2 H).

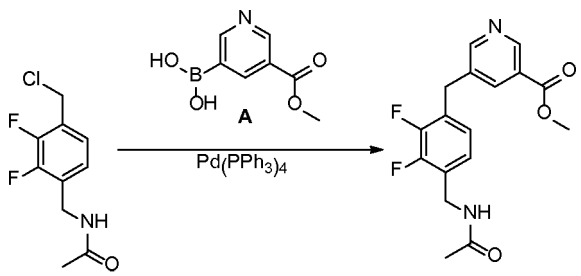
Example 143: Preparation of 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6- fluoro-1 H-indol-5-yl)methyl)nicotinamide



5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide

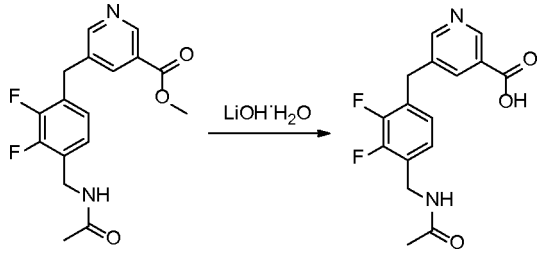


To a solution of N-(2,3-difluoro-4-hydroxymethyl-benzyl)-acetamide (500 mg, 2.326 mmol, 1 eq) in $CHCl_3$ (15 mL) was added $SOCl_2$ (0.21 mL) and the mixture was refluxed under heating for 1 h. The solvent was evaporated and the residue was used for the next step directly.

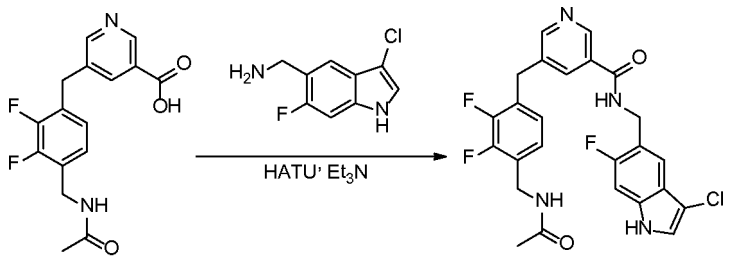


To a solution of the above compound and boronic acid **A** (524 mg, 2.894 mmol, 1.2 eq) in dioxane (16 mL) and water (4 mL) was added $Pd(PPh_3)_4$ and Na_2CO_3 (740 mg, 6.98 mmol, 3 eq). The mixture was stirred at 95 °C for 1 h under nitrogen. The solvent was removed in vacuo and the residue was diluted with water and was extracted with EA. The combined extracts were dried and concentrated. The residue was purified by

chromatography on a silica gel column (PE/EA = 2/1) to give 5-[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-nicotinic acid methyl ester (640 mg, 88%) as a yellow solid.

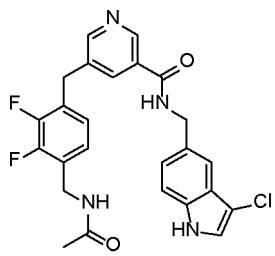


To a solution of 5-[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-nicotinic acid methyl ester (640 mg, 1.94 mmol, 1.0 eq) in THF (18 mL)/ H_2O (2 mL) was added LiOH.H_2O (90 mg, 2.14 mmol, 1.1 eq). The mixture was stirred at 40 °C for 30 min and the solvent was removed in vacuo. The residue was diluted with water and the mixture was acidified to pH 5 with 1 N HCl solution. The mixture was extracted with DCM and the combined extracts were concentrated in vacuo. The residue (420 mg, 67% yield) as yellow solid was directly used without further purification.

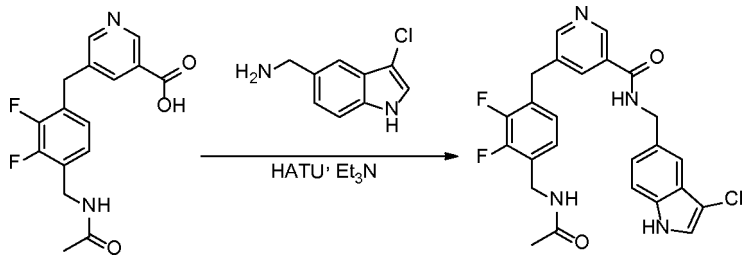


To a solution of 5-[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-nicotinic acid (68 mg, 0.214 mmol, 1.0 eq) and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (50 mg, 0.214 mmol, 1.0 eq) in DCM (4 mL) was added HATU (98 mg, 0.257 mmol, 1.2 eq) and Et_3N (0.12 mL, 0.856 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 20/ 1) to give 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)nicotinamide (52 mg, 50%) as a white solid. LRMS ($M+H^+$) m/z calculated 501.1, found 501.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.87 (d, 1 H), 8.60 (d, 1 H), 8.12 (s, 1 H), 7.54 (d, 1 H), 7.25 (s, 1 H), 7.14 (d, 1 H), 7.11-7.06 (m, 2 H), 4.72 (s, 2 H), 4.41 (s, 2 H), 4.15 (s, 2 H), 1.96 (s, 3 H).

Example 144: Preparation of 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-indol- 5-yl)methyl)nicotinamide

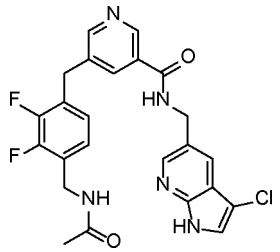


5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide

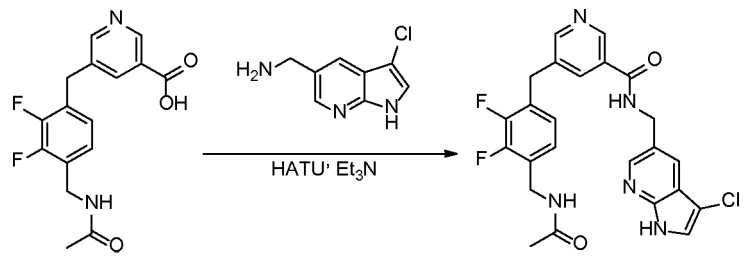


To a solution of 5-[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-nicotinic acid (68 mg, 0.214 mmol, 1.0 eq) and C-(3-Chloro-1 H-indol-5-yl)-methylamine (50 mg, 0.214 mmol, 1.0 eq) in DCM (4 mL) was added HATU (98 mg, 0.257 mmol, 1.2 eq) and Et_3N (0.12 mL, 0.856 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 20/ 1) to give 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide (60 mg, 55%) as a white solid. LRMS ($M+H^+$) m/z calculated 483.1, found 483.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.86 (d, 1 H), 8.56 (d, 1 H), 8.09 (s, 1 H), 7.52 (s, 1 H), 7.35 (d, 1 H), 7.24 (s, 1 H), 7.20 (dd, 1 H), 7.09-7.00 (m, 2 H), 4.66 (s, 2 H), 4.39 (s, 2 H), 4.06 (s, 2 H), 1.97 (s, 3 H).

Example 145: Preparation of 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-pyrrolo [2,3-b]pyridin-5-yl)methyl)nicotinamide



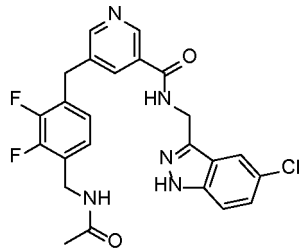
5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)nicotinamide



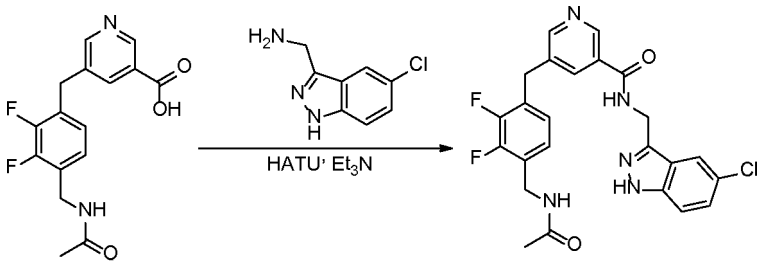
To a solution of 5-[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-nicotinic acid (70 mg, 0.219 mmol, 1.0 eq) and C-(3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)-methylamine (48 mg, 0.219 mmol, 1.0 eq) in DCM (4 mL) was added HATU (100 mg, 0.263 mmol, 1.2 eq) and Et_3N (0.12 mL, 0.876 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 10/ 1) to give 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)nicotinamide (66 mg, 63%) as a white solid. LRMS ($M+H^+$) m/z calculated 484.1, found 484.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.88 (d, 1 H), 8.61

(d, 1 H), 8.34 (d, 1 H), 8.11 (s, 1 H), 7.01 (d, 1 H), 7.44 (s, 1 H), 7.13-7.05 (m, 2 H), 4.72 (s, 2 H), 4.41 (s, 2 H), 4.15 (s, 2 H), 1.96 (s, 3 H).

Example 146: Preparation of 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((5-chloro-1H-indazol- 3-yl)methyl)nicotinamide

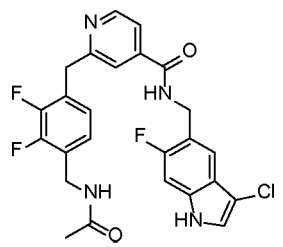


5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-*N*-((5-chloro-1*H*-indazol-3-yl)methyl)nicotinamide

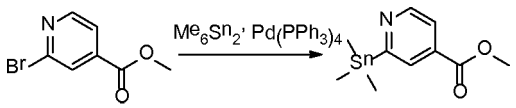


To a solution of 5-[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-nicotinic acid (70 mg, 0.219 mmol, 1.0 eq) and C-(5-chloro-1 H-indazol-3-yl)-methylamine (56 mg, 0.219 mmol, 1.0 eq) in DCM (4 mL) was added HATU (100 mg, 0.263 mmol, 1.2 eq) and Et_3N (0.15 mL, 1.1 mmol, 5 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 10/ 1) to give 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)nicotinamide (65 mg, 61%) as a white solid. LRMS ($M+H^+$) m/z calculated 484.1, found 484.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.08 (s, 1 H), 9.31 (s, 1 H), 8.90 (s, 1 H), 8.65 (s, 1 H), 8.34 (s, 1 H), 8.04 (s, 1 H), 7.91 (s, 1 H), 7.53 (d, 1 H), 7.34 (d, 1 H), 7.16-7.05 (m, 2 H), 4.78 (s, 2 H), 4.26 (s, 2 H), 4.09 (d, 2 H), 1.84 (s, 3 H).

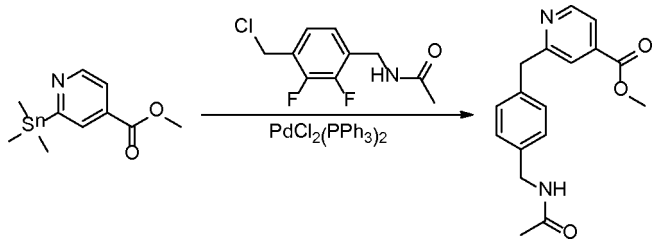
Example 147: Preparation of 2-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6- fluoro-1H-indol-5-yl)methyl)pyridine-4-carboxamide



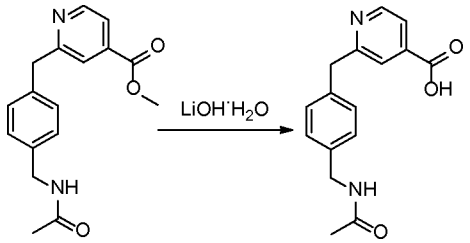
2-(4-(acetamidomethyl)-2,3-difluorobenzyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)isonicotinamide



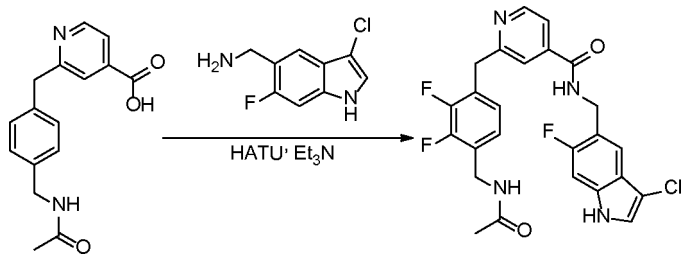
A solution of 2-bromo-isonicotinic acid methyl ester (1.2 g, 5.58 mmol, 1eq), Me_6Sn_2 (1.4 mL, 6.70 mmol, 1.2 eq) and $Pd(PPh_3)_4$ (324 mg, 0.28 mmol, 0.05 eq) in toluene (28 mL) was heated at 80 °C for 12 h under nitrogen atmosphere. The mixture was cooled to rt and filtered through a pad of celite. The filtrate was concentrated and the residue was directly used.



To a solution of 2-trimethylstannanyl-isonicotinic acid methyl ester (290 mg, 0.97 mmol, 1.5 eq) and N-(4-chloromethyl-2,3-difluoro-benzyl)-acetamide (150 mg, 0.64 mmol, 1eq) in dioxane (10 mL) was added $PdCl_2(PPh_3)_2$ (23 mg, 0.032 mmol, 0.05 eq). The mixture was stirred at 90 °C for 2 h under nitrogen. The mixture was cooled to rt and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 20/ 1) to give 2-[4-(acetylamino-methyl)-benzyl]-isonicotinic acid methyl ester (100 mg, 47%) as an off-white solid.



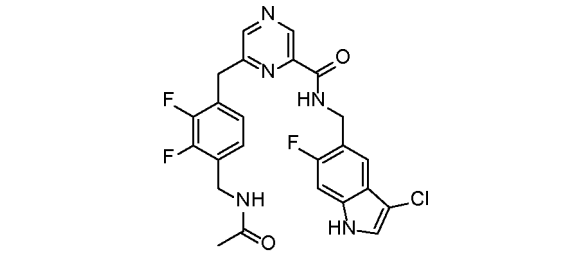
To a solution of 2-[4-(acetylamino-methyl)-benzyl]-isonicotinic acid methyl ester (100 mg, 0.30 mmol, 1.0 eq) in THF (5 mL)/ H_2O (1 mL) was added $LiOH.H_2O$ (14 mg, 0.33 mmol, 1.1 eq). The mixture was stirred at 40 °C for 30 min and was acidified to pH 5~6 with 1N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification.



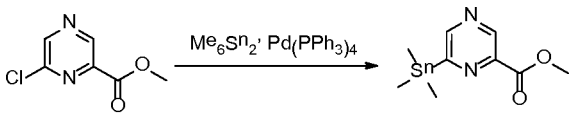
To a solution of the above crude product and C-(3-chloro-6-fluoro-1H-indol-5-yl)-methylamine (60 mg, 0.27 mmol, 0.9 eq) in DCM (4 mL) was added HATU (137 mg, 0.36 mmol, 1.2 eq) and Et_3N (0.17 mL, 1.2 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 20/ 1) to give 2-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)pyridine-4-carboxamide (65 mg, 43% yields for 2 steps) as an off white solid. LRMS ($M+H^+$) m/z calculated 501.1, found 501.1. ^1H NMR (CD_3OD, 400

MHz) δ 8.34 (d, 1 H), 7.45 (s, 1 H), 7.40 (d, 1 H), 7.29 (d, 1 H), 7.01 (s, 1 H), 6.90 (d, 1 H), 6.85- 6.76 (m, 2 H), 4.47 (s, 2 H), 4.17 (s, 2 H), 4.00 (s, 2 H), 1.75 (s, 3 H).

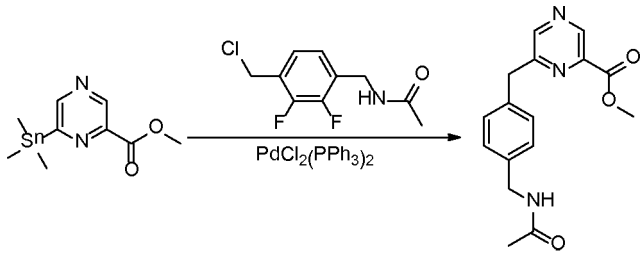
Example 148: Preparation of 6-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6- fluoro-1H-indol-5-yl)methyl)pyrazine-2-carboxamide



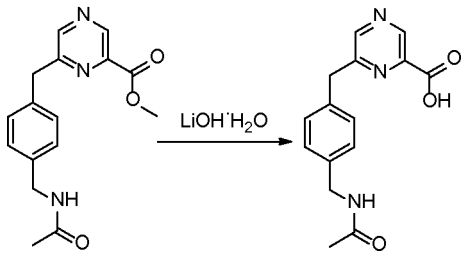
6-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)pyrazine-2-carboxamide



A solution of 6-chloro-pyrazine-2-carboxylic acid methyl ester (690 mg, 4.0 mmol, 1eq), Me_6Sn_2 (1.0 mL, 4.82 mmol, 1.2 eq) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol, 0.05 eq) in toluene (20 mL) was heated at 80 °C for 12 h under nitrogen atmosphere. The mixture was cooled to rt and was concentrated. The residue was purified by chromatography on a silica gel column (EA/ PE = 1/5) to give 6-trimethylstannanyl-pyrazine-2-carboxylic acid methyl ester (360 mg, 30%) as a yellow oil.

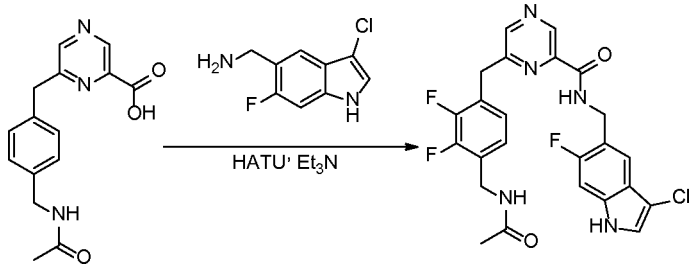


To a solution of 6-trimethylstannanyl-pyrazine-2-carboxylic acid methyl ester (264 mg, 0.88 mmol, 1.2 eq) and N-(4-chloromethyl-2,3-difluoro-benzyl)-acetamide (170 mg, 0.73 mmol, 1eq) in dioxane (10 mL) was added $PdCl_2(PPh_3)_2$ (26 mg, 0.036 mmol, 0.05 eq). The mixture was stirred at 95 °C for 2 h under nitrogen. The mixture was cooled to rt and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 20/ 1) to give 6-[4-(acetylamino-methyl)-benzyl]-pyrazine-2-carboxylic acid methyl ester (132 mg, 52%) as a yellow solid.



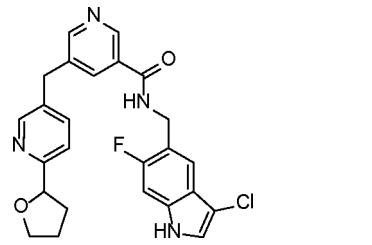
To a solution of 6-[4-(acetylamino-methyl)-benzyl]-pyrazine-2-carboxylic acid methyl ester (100 mg, 0.336 mmol, 1.0 eq) in THF (5 mL)/ H_2O (1 mL) was added $LiOH.H_2O$ (16 mg, 0.369 mmol, 1.1 eq). The mixture

was stirred at 40 °C for 30 min and was acidified to pH 5~6 with 1N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification.

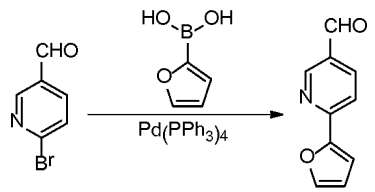


To a solution of the above crude product and C-(3-chloro-6-fluoro-1H-indol-5-yl)-methylamine (46 mg, 0.194 mmol, 1 eq) in DCM (4 mL) was added HATU (153 mg, 0.403 mmol, 1.2 eq) and Et_3N (0.19 mL, 1.344 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 10/ 1) to give 6-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)pyrazine-2-carboxamide (70 mg, 64% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 502.1, found 502.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.39 (s, 1 H), 9.13-9.11 (m, 1 H), 9.06 (s, 1 H), 8.79 (s, 1 H), 8.36-8.32 (m, 1 H), 7.50 (d, 1 H), 7.45 (d, 1 H), 7.22 (d, 1 H), 7.20-7.04 (m, 2 H), 4.63 (d, 2 H), 4.30 (s, 2 H), 4.26 (d, 2 H), 1.84 (s, 3 H).

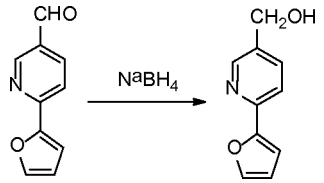
Example 149: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((6- (tetrahydrofuran-2-yl)pyridin-3-yl)methyl)nicotinamide



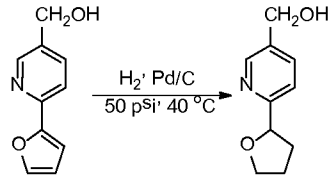
N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-5-((6-(tetrahydrofuran-2-yl)pyridin-3-yl)methyl)nicotinamide



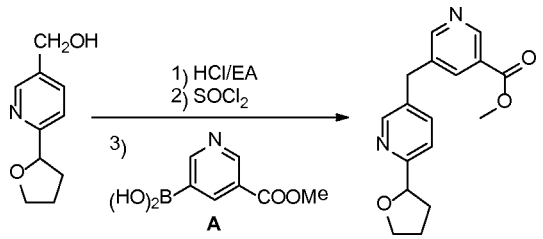
To a solution of 6-bromo-pyridine-3-carbaldehyde (5.58 g, 30 mmol, 1 eq) and furan-2-boronic acid (3.36 g, 30 mmol, 1 eq) in dioxane (40 mL) and water (10 mL) was added $Pd(PPh_3)_4$ (1.73 g, 1.5 mmol, 0.05 eq) and Na_2CO_3 (9.54 g, 90 mmol, 3 eq). The mixture was stirred at 95 °C for 2 h under nitrogen. The mixture was allowed to cool to rt The solvent was removed in vacuo and the residue was diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (EA/ PE = 1/ 5) to give 6-furan-2-yl-pyridine-3-carbaldehyde (4.50 g, 86%) as a yellow solid.



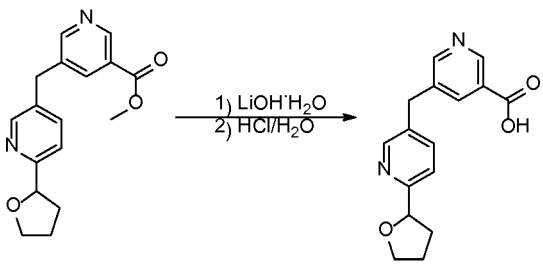
To a solution of 6-furan-2-yl-pyridine-3-carbaldehyde (2.2 g, 11.56 mmol, 1 eq) in MeOH (20 mL) was added $NaBH_4$ (1.0 g, 26.59 mmol, 2 eq) portionwise at 0 °C. Then the mixture was stirred at rt for 1 h and diluted with saturated aqueous NH_4Cl solution. The combined mixture was concentrated to remove MeOH and the resultant aqueous solution was extracted with DCM, dried and concentrated to give (6-furan-2-yl-pyridin-3-yl)-methanol (1.87 g, 93%).



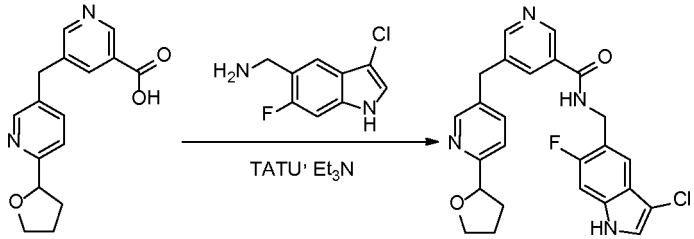
To a solution of (6-furan-2-yl-pyridin-3-yl)-methanol (800 mg, 4.57 mmol, 1 eq) in MeOH (40 mL) was added 10% Pd/C (200 mg). The mixture was stirred at 40 °C for 30 h under the presence of H_2. Pd/C was removed by filtration and the filtrate was concentrated. The residue was purified by chromatography on a silica gel column (EA/ PE = 1/ 1) to give [6-(tetrahydro-furan-2-yl)-pyridin-3-yl]-methanol (540 mg, 66%) as a colorless oil.



To a solution of [6-(tetrahydro-furan-2-yl)-pyridin-3-yl]-methanol (500 mg, 2.79 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 0.5 h and the excess reagent was removed by evaporation. The residue was treated with $SOCl_2$ (7 mL) and the mixture was heated under reflux for 1 h. The excess reagent was removed in vacuo. To a solution of the above residue and boronic acid **A** (2.8 mmol, 1 eq) in dioxane (14 mL) and water (3.5 mL) was added Na_2CO_3 (1.2 g, 11.2 mmol, 4 eq) and $Pd(PPh_3)_4$ (162 mg, 0.14 mmol, 0.05 eq). The mixture was stirred at 95 °C for 2 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (EA/ PE = 1/15) to give 5-[6-(tetrahydro-furan-2-yl)-pyridin-3-ylmethyl]-nicotinic acid methyl ester (690 mg, 83%) as a yellow solid.

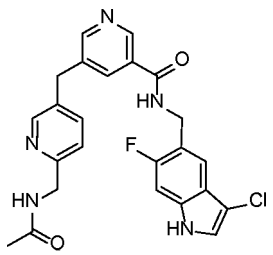


To a solution of 5-[6-(tetrahydro-furan-2-yl)-pyridin-3-ylmethyl]-nicotinic acid methyl ester (100 mg, 0.194 mmol, 1.0 eq) in THF (5 mL)/ H_2O (1 mL) was added LiOH.H_2O (9 mg, 0.213 mmol, 1.1 eq). The mixture was stirred at 40 °C for 30 min and was acidified to pH 5~6 with 1N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification.

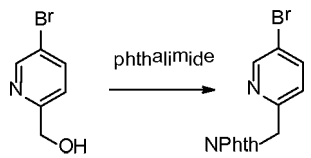


To a solution of the above crude product and C-(3-chloro-6-fluoro-1H-indol-5-yl)-methylamine (46 mg, 0.194 mmol, 1 eq) in DCM (4 mL) was added HATU (89 mg, 0.233 mmol, 1.2 eq) and Et_3N (0.11 mL, 0.776 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 10/ 1) to give N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((6-(tetrahydrofuran-2-yl)pyridin-3-yl)methyl)nicotinamide (40 mg, 41% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 465.1, found 465.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.74 (d, 1 H), 8.48 (d, 1 H), 8.28 (d, 1 H), 7.98 (t, 1 H), 7.55 (dd, 1 H), 7.39 (d, 1 H), 7.30 (d, 1 H), 7.11 (s, 1 H), 7.00 (d, 1 H), 4.81-4.77 (m, 1 H), 4.57 (s, 2 H), 3.98 (s, 2 H), 3.98-3.93 (m, 1 H), 3.84-3.78 (m, 1 H), 2.30-2.21 (m, 1 H), 1.90-1.82 (m, 2 H), 1.77-1.70 (m, 1 H).

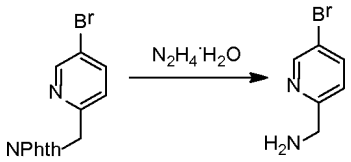
Example 150: Preparation of 5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro- 6-fluoro-1H-indol-5-yl)methyl)nicotinamide



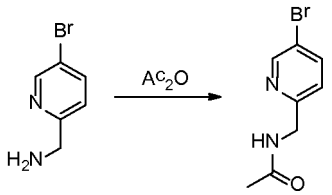
5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide



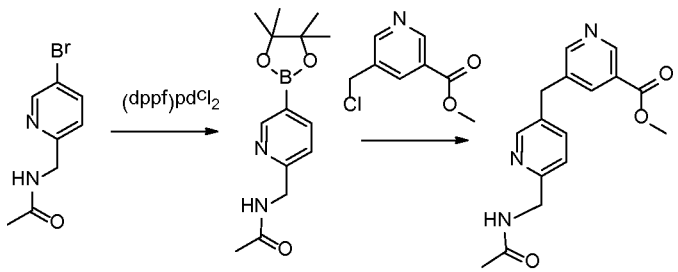
To a solution of (5-bromo-pyridin-2-yl)-methanol (5 g, 26.6 mmol, 1.0 eq), Ph_3P (8.38 g, 32.0 mmol, 1.2eq), phthalimide (4.69 g, 32.0 mmol, 1.2 eq) in anhydrous THF under nitrogen was added DIAD (6.46 g, 32.0 mmol, 1.2eq) .The mixture was stirred at rt for 12 h and the excess reagent was removed in vacuo. The mixture was extracted with EA and purified by flash column chromatography on silica gel (PE) to give 2-(5-bromo-pyridin-2-ylmethyl)-isoindole-1,3-dione (8 g, 95%) as white solid.



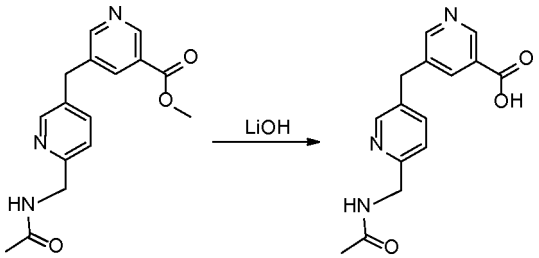
To a solution of 2-(5-bromo-pyridin-2-ylmethyl)-isoindole-1,3-dione (8 g, 25 mmol, 1.0 eq) in EtOH (50 mL) was added $N_2H_4.H_2O$ (8 mL). The mixture was stirred at 60 °C for 4 h. The precipitate was removed by filtration. The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (PE) to give C-(5-bromo -pyridin-2-yl)-methylamine (4.7 g, 99%) as an orange solid.



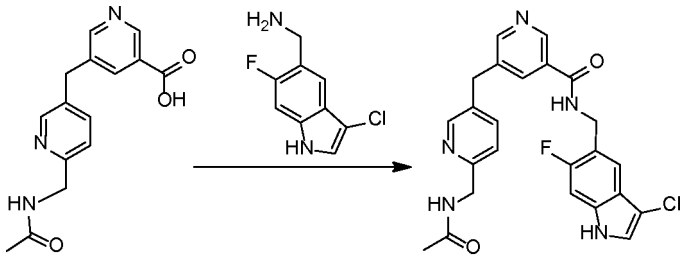
To a solution of compound C-(5-bromo-pyridin-2-yl)-methylamine (4.7 g, 25 mmol, 1 eq) in DCM (100 mL) was added Ac_2O (5.13 g, 50 mmol, 2 eq) followed by Et_3N (5.13 g, 50 mmol, 2eq) at 0 °C under nitrogen. After the addition, the mixture was stirred at rt overnight. The mixture was poured into water and extracted with EA. The organic solution was dried and concentrated. The residue was purified by flash column chromatography on silica gel (EA) to give N-(5-bromo-pyridin-2-ylmethyl)-acetamide (5.29 g, 91.8%) as a white solid.



To a solution of compound N-(5-bromo-pyridin-2-ylmethyl)-acetamide (0.5 g, 2.2 mmol, 1 eq) and $B_2(Pin)_2$ (0.67 g, 2.6 mmol, 1.2 eq) in dioxane (25 mL) was added KOAc (0.65g, 6.6 mmol, 3 eq) and $(dppf)PdCl_2.CH_2Cl_2$ (90 mg, 0.11 mmol, 0.05 eq). The mixture was stirred at 95 °C under nitrogen for 12 h and cool down, to get N-[5-(4,4,5,5N -[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-ylmethyl]-acetamide as a crude compound. To a solution of compound N-[5-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl) -pyridin-2-ylmethyl]-acetamide and 5-chloromethyl-nicotinic acid methyl ester (0.487 g, 2.2 mmol, 1 eq) in dioxane (20 mL) and water (5 mL) was added Na_2CO_3 (0.7 g, 6.6 mmol, 3 eq), and $(dppf)PdCl_2.CH_2Cl_2$ (90 mg, 0.11 mmol, 0.05 eq). The mixture was stirred at 100 °C for 3 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ CH_3OH = 10/1) to give 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl]-nicotinic acid methyl ester (0.59 g, 91%) as a yellow oil.

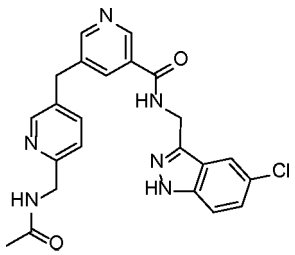


To a solution of compound 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl] -nicotinic acid methyl ester (2.37 g, 7.9 mmol, 1 eq) in THF (90 mL) and water (10 mL) was added LiOH (0.366 g, 8.7 mmol, 1.1 eq). The mixture was stirred at 40 °C for 3 h and was acidified to pH 5~6 with 1N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification

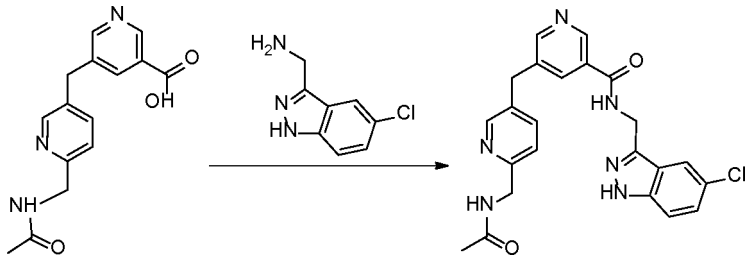


To a solution of compound 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl]-nicotinic acid (60 mg, 0.21 mmol, 1 eq) and C-(3-chloro-6-fluoro-1 H-indol-5-yl) - methylamine (50 mg, 0.21 mmol, 1 eq) in DMF (4 mL) was added HATU (88 mg, 0.231 mmol, 1.1 eq) and Et_3N (0.1 mL, 0.84 mmol, 4 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ CH_3OH = 10/1) to give 5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)nicotinamide (10 mg, 10%) as an off white solid. LRMS ($M+H^+$) m/z calculated 466.1, found 466.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.1(s, 1 H) 9.3 (t, 1 H), 8.9 (s, 1 H), 8.6 (s, 1 H), 8.5 (s, 1 H), 8.36 (t, 1 H), 8.1 (s, 1 H),7.9 (s, 1 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 7.3 (d, 1 H), 7.2 (d, 1 H), 4.8 (d, 2 H), 4.3 (d, 2 H), 4.0 (s, 2 H), 1.9 (s, 3 H).

Example 151: Preparation of 5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide

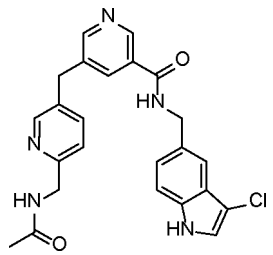


5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide

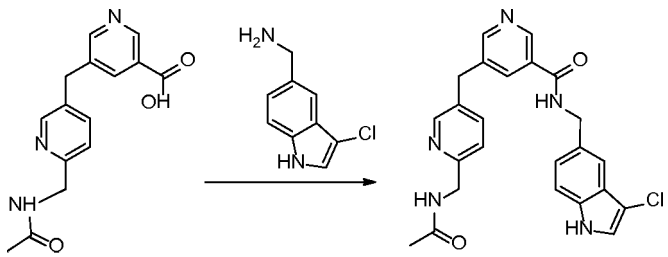


To a solution of compound 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl]-nicotinic acid (131 mg, 0.46 mol,1 eq) and C-(5-chloro-1 H-indazol-3-yl)-methylamine (100 mg, 0.46 mmol, 1 eq) in DMF (4 mL) was added HOBT (75 mg, 0.552 mmol, 1.2 eq), EDCI (106 mg, 0.552 mmol, 1.2 eq) and Et_3N (0.186 g, 1.84 mmol, 4 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ CH_3OH = 10/1) to give 5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1 H-indazol-3-yl)methyl)nicotinamide (16 mg, 8%) as an off white solid. LRMS (M+H+) m/z calculated 449.1, found 449.1. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.8 (d, 1 H), 8.6 (d, 1 H), 8.4 (d, 1 H), 8.2 (s, 1 H), 7.9 (t, 1 H), 7.6 (s, 1 H), 7.45 (m, 1 H), 7.36-7.34 (d, 1 H), 7.25-7.2 (m, 2 H), 4.75-4.74 (d, 2 H), 4.52-4.51 (d, 2 H), 4.02 (s, 1 H), 2.06 (s, 3 H).

Example 152: Preparation of 5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



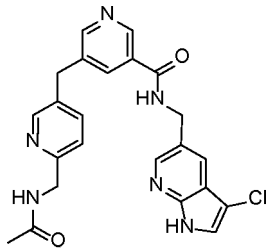
5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide



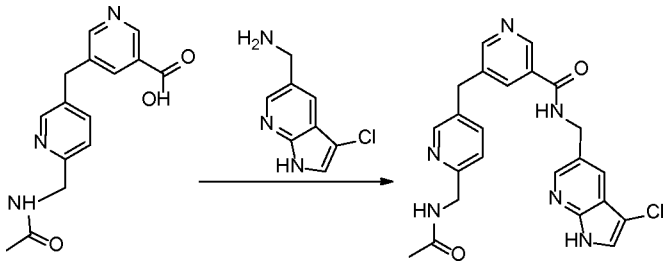
To a solution of 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl] (131mg, 0.46 mmol, 1 eq) and C-(3-chloro-1 H-indol-5-yl)-methylamine (100 mg, 0.46 mmol, 1 eq) in DMF (4 mL) was added HOBT (75 mg, 0.552 mmol, 1.2 eq), EDCI (106 mg, 0.552 mmol, 1.2 eq) and Et_3N (0.186 g, 1.84 mmol, 4 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ CH_3OH = 10/1) to give 5-[6-(acetylamino -methyl)-pyridin-3-ylmethyl]-N-(3-chloro-1 H-indol-5-ylmethyl)-nicotinamide (52 mg, 25% yield) as an off-white solid. LRMS

(M+H+) m/z calculated 448.1, found 448.1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.8 (d, 1 H), 8.6 (d, 1 H), 8.4 (d, 1 H), 8.2 (s, 1 H), 7.9 (t, 1 H), 7.6 (s, 1 H), 7.45 (m, 1 H), 7.36-7.34 (d, 1 H), 7.25-7.24 (m, 2 H), 4.75-4.74 (m, 2 H), 4.52-4.51 (m, 2 H), 4.02 (s, 1 H), 2.06 (s, 3 H).

Example 153: Preparation of 5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-pyrrolo [2,3-b]pyridin-5-yl)methyl)nicotinamide

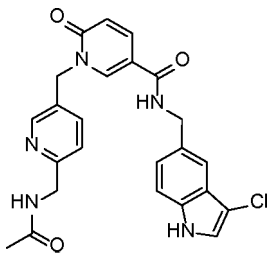


5-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)nicotinamide

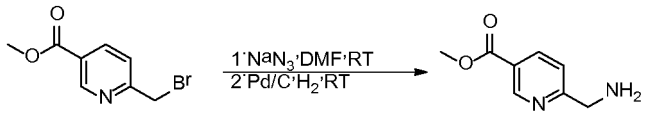


To a solution of 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl] (131 mg, 0.46 mmol, 1 eq) and C-(3-chloro-1 H-pyrrolo[2,3-b]pyridin-5-yl)-methylamine (100 mg, 0.46 mmol, 1 eq) in DMF (4 mL) was added HOBT (75 mg, 0.552 mmol, 1.2 eq), EDCI (106 mg, 0.552 mmol, 1.2 eq) and Et_3N (0.186 g, 1.84 mmol, 4 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ CH_3OH = 10/1) to give 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl]-N-(3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-nicotinamide (42 mg, 20%) as an off white solid. LRMS ($M+H^+$) m/z calculated 449.1, found 449.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.9 (s, 1 H), 9.2 (t, 1 H), 8.9 (d, 1 H), 8.7 (d, 1 H), 8.5 (s, 1 H), 8.4 (t, 1 H), 8.3 (d, 1 H), 8.1 (s, 1 H), 7.9 (s, 1 H), 7.67 (d, 1 H), 7.65-7.62 (m, 1 H), 7.21 (d, 1 H), 4.59 (d, 2 H), 4.29 (d, 2 H), 4.0 (s, 2 H), 1.9 (s, 3 H).

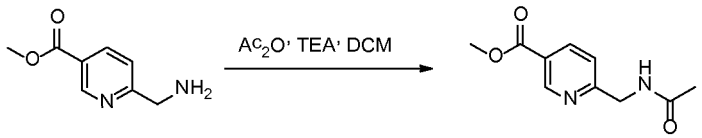
Example 154: Preparation of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol- 5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



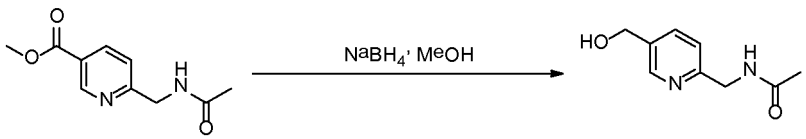
1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



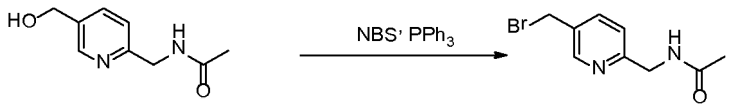
To a solution of methyl 6-(bromomethyl)nicotinate (9.0 g, 39.12 mmol, 1.0 eq) in DMF (60 mL) was added NaN_3 (3.8 g, 58.68 mmol, 1.5 eq). The resultant mixture was stirred overnight at room temperature. The reaction mixture was added water and extracted with DCM, and the organic lay was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in MeOH, and 10% of Pd/C (500 mg) was added. The resultant mixture was stirred overnight at room temperature under H_2 (1 atm.). The reaction mixture was concentrated. The residue was purified by column chromatography (DCM/ MeOH = 10/1) to give methyl 6-(aminomethyl)nicotinate (3.0 g, 46%) as a brown solid.



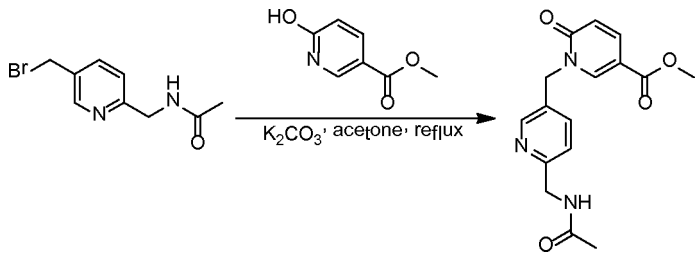
To a solution of methyl 6-(aminomethyl)nicotinate (3.0 g, 18.05 mmol, 1.0 eq) in DCM (30 mL) was added TEA (3.7 g, 36.11 mmol, 2.0 eq). The reaction mixture was cooled to 0 °C, and then Ac_2O (3.7 g, 36.11 mmol, 2.0 eq) was added dropwise over period of 5 min. The resultant mixture was warmed to rt and stirred for 1 h and the reaction mixture was concentrated. The residue was purified by column chromatography (DCM/ MeOH = 20/ 1) to give methyl 6-(acetamido methyl)nicotinate (3.6 g, 95%) as a yellow solid.



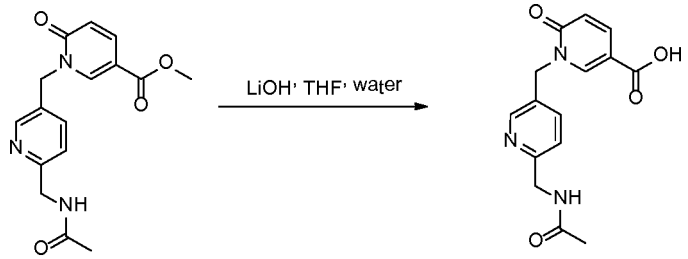
To a solution of methyl 6-(acetamidomethyl)nicotinate (3.6 g, 17.29 mmol, 1.0 eq) in MeOH (50 mL) was added $NaBH_4$ (1.3 g, 34.58 mmol, 2.0 eq) at 0 °C and then the reaction mixture was warmed to rt and kept stirring overnight. The reaction mixture was concentrated and the residue was purified by column (DCM/ MeOH = 10/ 1) to give N-((5-(hydroxymethyl)pyridine -2-yl)methyl)acetamide (2.2 g, 71%) as a yellow solid.



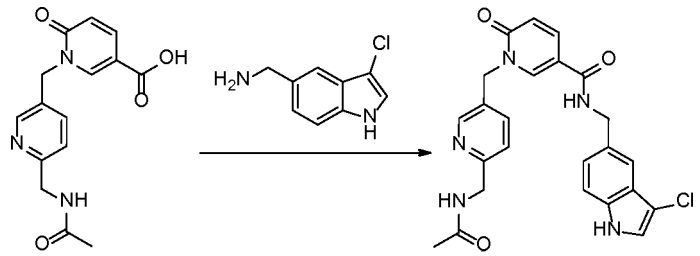
To a stirred solution of N-((5-(hydroxymethyl)pyridin-2-yl)methyl)acetamide (2.2 g, 12.21 mol, 1.0 eq) in DCM (100 mL) was added PPh_3 (4.8 g, 18.31 mmol, 1.5 eq) followed by NBS (2.6 g, 14.65 mmol, 1.2 eq) at 0 °C under N_2. The reaction mixture was warmed to room temperature and kept stirring for 1 h. The reaction was quenched with water (100 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (DCM/ MeOH = 15/ 1) to give N-((5-(bromomethyl)pyridin-2-yl)methyl)acetamide (1.7 g, 57%) as a pink solid. LRMS ($M+H^+$) m/z calculated 242, 244, found 243, 245 $[M+H]^+$.



To a solution of methyl 6-hydroxynicotinate (0.63 g, 4.11 mmol, 1.0 eq) in acetone (50 mL) was added K_2CO_3 (1.1 g, 8.22 mmol, 2.0 eq) followed by N-((5-(bromomethyl)pyridin-2-yl) methyl)acetamide (1.0 g, 4.11 mmol, 1.0 eq). The resultant mixture was heated to reflux and kept stirring overnight. The reaction mixture was concentrated and the residue was purified by column chromatography (DCM/ MeOH = 15/ 1) to give methyl 1-((6-(acetamidomethyl)pyridin-3- yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (1.1 g, 85%) as a pink solid.



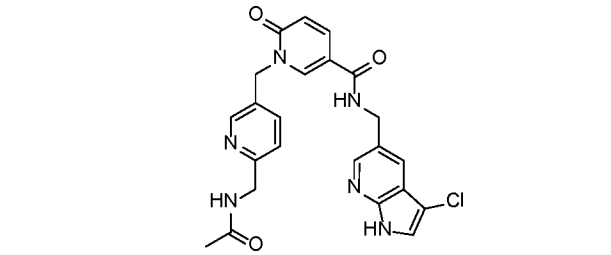
To a solution of methyl 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-6-oxo-1,6-dihydro pyridine-3-carboxylate (1.0 g, 3.17 mmol, 1.0 eq) in THF/water (5 mL/5 mL) was added LiOH.H_2O (0.2 g, 4.76 mmol, 1.5 eq). The resultant mixture kept stirring for 2 h. LRMS showed the SM was consumed and the organic solvent was removed. The reaction mixture was acidified to pH 5 by HCl (1 N), and then the mixture were concentrated to give the crude1-((6-(acetamidomethyl)pyridin-3- yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.4 g) as a pink solid, which was used directly without further purification.



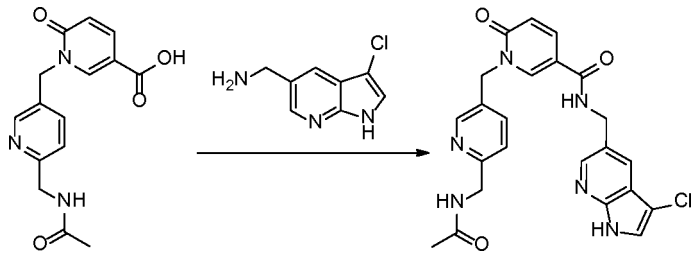
To a solution of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-6-oxo-1,6-dihydropyridine -3-carboxylic acid (140 mg, crude) in DMSO (10 mL) was added (3-chloro-1 H-indol-5-yl)methanamine hydrochloride (72 mg, 0.33 mmol, 1.0 eq) followed by EDCI (76 mg, 0.40 mmol, 1.2 eq), HOBT (54 mg, 0.40 mmol, 1.2 eq) and TEA (100 mg, 0.99 mmol, 3.0 eq). The reaction mixture was heated to 30 °C and kept stirring for overnight. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (DCM/ MeOH = 10/ 1) to give 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1 H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (25 mg, 16%) as a white solid. LRMS ($M+H^+$) m/z calculated 464.1 found/ 464.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.86 (s, 3 H), 4.29 (d, 2 H), 4.52 (d, 2 H), 5.16 (s, 2 H), 6.45

(d, 1 H), 7.14 (d, 1 H), 7.25(d, 1 H), 7.36 (d, 1 H), 7.41 (s, 1 H), 7.49 (d, 1 H), 7.70(d, 1 H), 7.92 (d, 1 H), 8.39 (t, 1 H), 8.53 (d, 1 H), 8.80 (t, 1 H), 11.32 (s, 1 H).

Example 155: Preparation of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

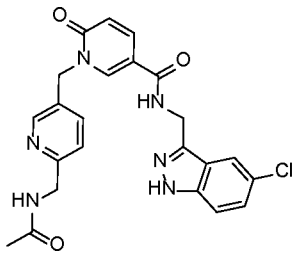


1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

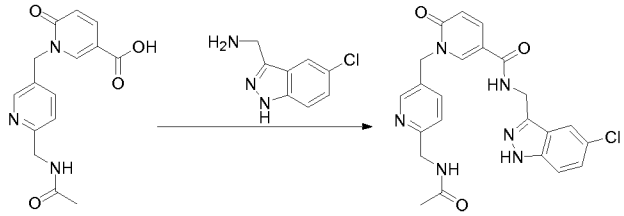


To a solution of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-6-oxo-1,6-dihydropyridine -3-carboxylic acid (140 mg, crude) in DMSO (10 mL) was added (3-chloro-1 H-pyrrolo[2,3-b]pyridine -5-yl)methanamine hydrochloride (72 mg, 0.33 mmol, 1.0 eq) followed by EDCI (76 mg, 0.40 mmol, 1.2 eq), HOBT (54 mg, 0.40 mmol, 1.2 eq) and TEA (100 mg, 0.99 mmol, 3.0 eq). The reaction mixture was heated to 30 °C and kept stirring for overnight. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (DCM/ MeOH = 10/ 1) to give 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (32 mg, 8%) as a white solid. LRMS ($M+H^+$) m/z calculated 465.1, found 465.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.86 (s, 3 H), 4.29 (d, 2 H), 4.54 (d, 2 H), 5.15 (s, 2 H), 6.44 (d, 1 H), 7.24 (d, 1 H), 7.67-7.70 (m, 2 H), 7.86-7.92 (m, 2 H), 8.29(d, 1 H), 8.40 (t, 1 H), 8.54 (d, 1 H), 8.85 (t, 1 H), 11.95 (s, 1 H).

Example 156: Preparation of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1 H-indazol- 3-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

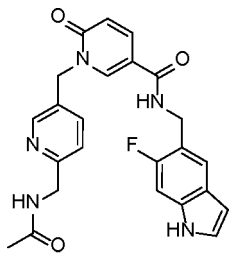


1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

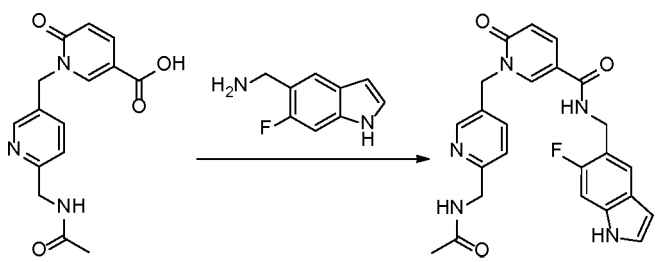


To a solution of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-6-oxo-1,6-dihydropyridine -3-carboxylic acid (140 mg, crude) in DMSO (10 mL) was added (5-chloro-1 H-indazol-3-yl)methanamine hydrochloride (72 mg, 0.33 mmol, 1.0 eq) followed by EDCI (76 mg, 0.40 mmol, 1.2 eq), HOBT (54 mg, 0.40 mmol, 1.2 eq) and TEA (100 mg, 0.99 mmol, 3.0 eq). The reaction mixture was heated to 30 °C and kept stirring for overnight. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, concentrated. The residue was purified by column chromatography (DCM/ MeOH = 10/ 1) to give 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (12 mg, 8%) as a white solid. LRMS ($M+H^+$) m/z calculated 465.1, found 465.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 1.86 (s, 3 H), 4.28 (d, 2 H), 4.74 (d, 2 H), 5.15 (s, 2 H), 6.44 (d, 2 H), 7.24 (d, 1 H), 7.34 (d, 1 H), 7.53 (d, 1 H), 7.69 (d, 1 H), 7.90-7.93 (m, 2 H), 8.42 (t, 1 H), 8.52 (d, 1 H), 8.57 (d, 1 H), 8.92 (t, 1 H),13.09 (s, 1 H).

Example 157: Preparation of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((6-fluoro-1 H-indol-5-yl) methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



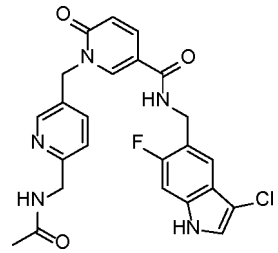
1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



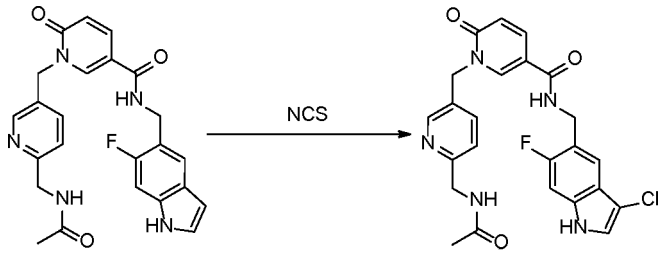
To a solution of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-6-oxo-1,6-dihydropyridine -3-carboxylic acid (300 mg, crude) in DMSO (20 mL) was added (6-fluoro-1H-indol-5-yl)meth anamine (164 mg, 1.00 mmol,

1.0 eq) followed by EDCI (228 mg, 1.20 mmol, 1.2 eq), HOBT (162 mg, 1.2 mmol, 1.2 eq) and TEA (304 mg, 3.00 mmol, 3.0 eq). The reaction mixture was purified by prep-HPLC to give 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (150 mg, 34%) as a white solid. LRMS ($M+H^+$) m/z calculated 448.1, found 448.1; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.86 (s, 3 H), 4.30 (d, 2 H), 4.52 (d, 2 H), 5.16 (s, 2 H), 6.40-6.46(m, 2 H), 7.16 (d, 1 H), 7.25(d, 1 H), 7.31 (d, 1 H), 7.49 (d, 1 H), 7.70 (d, 1 H), 7.93(d, 1 H), 8.41(t, 1 H), 8.53-8.57 (m, 2 H), 8.71 (t, 1 H), 11.10 (s, 1 H).

Example 158: Preparation of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-6- fluoro-1H-indol-5-yl) methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

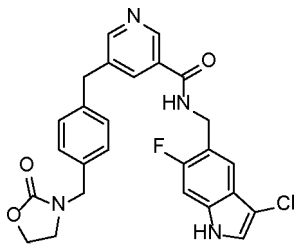


1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

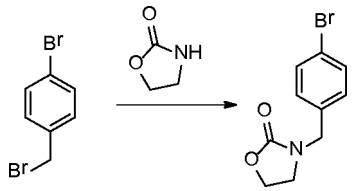


To a solution of 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((4-fluoro-1H-indol-5-yl) methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (100 mg, crude) in DCM (20 mL) was added NCS (164 mg, 1.00 mmol, 1.0 eq) at 0 °C. LRMS showed the SM was consumed. The reaction mixture was purified by prep-HPLC to give 1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (12 mg, 15%) as a white solid. LRMS ($M+H^+$) m/z calculated 482.1, found 482.1; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.86 (s, 3 H), 4.29 (d, 2 H), 4.54 (d, 2 H), 5.15 (s, 2 H), 6.45 (d, 1 H), 7.20-7.26 (m, 2 H), 7.44 (d, 1 H), 7.51 (s, 1 H), 7.69 (d, 1 H), 7.92 (d, 1 H), 8.40 (t, 1 H), 8.52 (d, 1 H), 8.56 (d, 1 H), 8.76 (t, 1 H), 11.39 (t, 1 H).

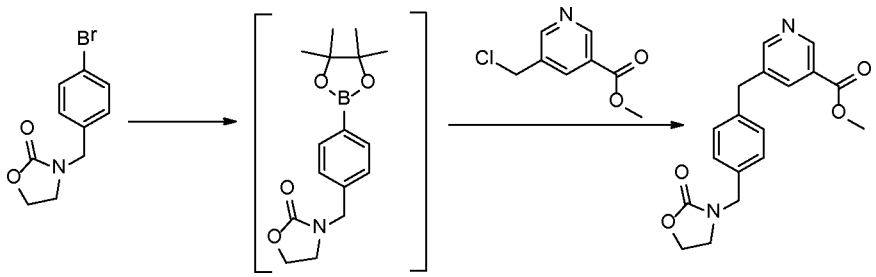
Example 159: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2- oxooxazolidin-3-yl)methyl)benzyl)nicotinamide



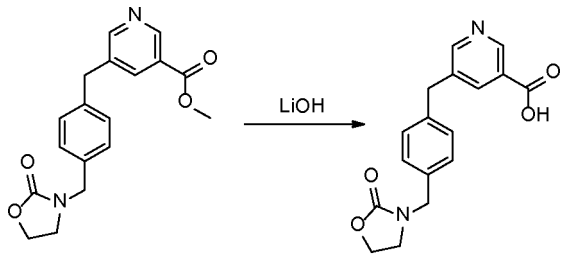
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide



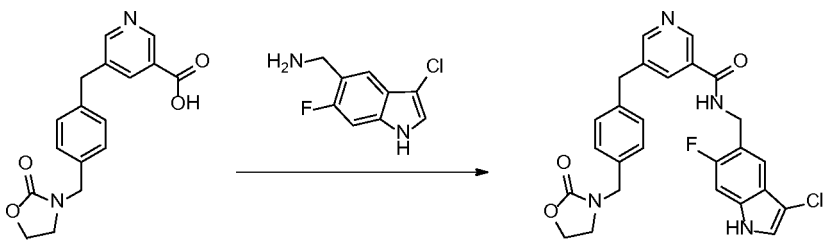
To a mixture of oxazolidin-2-one (1.0 g, 11.48 mmol, 1.0 eq) in DMF (30 mL) was added NaH (60%, 2.3 g, 57.40 mmol, 5 eq) at 0 °C. The resultant mixture was kept stirring for 30 min. The solution of 1-bromo-4-(bromomethyl)benzene (2.9 g, 11.48 mmol, 1 eq) in DMF (10 mL) was added and then the reaction mixture was warmed to rt, and kept stirring for 1 h. Water was added, and the mixture was extracted with DCM, and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (PE/ EA = 3/ 1) to give 3-(4-bromobenzyl)oxazolidin-2-one (2.2 g, 76%) as a white solid.



The mixture of 3-(4-bromobenzyl)oxazolidin-2-one (1.0 g, 3.91 mmol, 1.0 eq), $(Pin)_2B_2$(1.2 g, 4.69 mmol, 1.2 eq), $PdCl_2$(dppf).DCM (160 mg, 0.20 mmol, 0.05 eq), KOAc (1.1 g, 11.73 mmol, 3.0 eq) in dioxane (50 mL) was heated to 100 °C and kept stirring for 2 h under N_2. And then the reaction mixture was cooled to rt Then the compound methyl 5-(chloromethyl)nicotinate (726 mg, 3.91 mmol 1.0 eq), Na_2CO_3 (1.2 g, 11.73 mmol, 3.0 eq), $PdCl_2$(dppf). DCM (160 mg, 0.20 mmol, 0.05 eq) and water (5 mL) was added. The resultant mixture was heated to 100 °C and kept stirring for 2 h under N_2. The reaction mixture was concentrated. And the residue was purified by column chromatography (DCM/ MeOH = 30/ 1) to give methyl 5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinate (1.0 g, 77%) as a white solid.

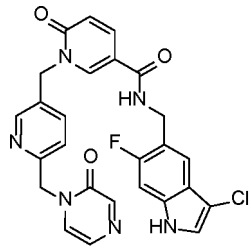


To a solution of methyl 5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinate (1.0 g, 3.06 mmol, 1.0 eq) in THF/water (10 mL/10 mL) was added LiOH.H_2O (193 mg, 4.60 mmol, 1.5 eq) and then the reaction mixture kept stirring for 2 h. The reaction mixture was concentrated to give the crude product 5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl) nicotinic acid (1.2 g) as a brown solid.

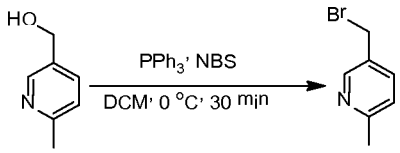


To a solution of 5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinic acid (100 mg, crude) in DMSO (10 mL) was added (3-chloro-6-fluoro-1 H-indol-5-yl)methanamine hydrochloride (75 mg, 0.32 mmol, 1.0 eq) followed by EDCI (74 mg, 0.38 mmol, 1.2 eq), HOBT (52 mg, 0.38 mmol, 1.2 eq) and TEA (97 mg, 0.96 mmol, 3.0 eq). The reaction mixture was heated to 30 °C and kept stirring overnight. LRMS showed the SM was consumed. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (DCM/ MeOH = 10/1) to give N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide (25 mg, 16%) as a white solid. LRMS ($M+H^+$) m/z calculated 493.1, found/ 493.1; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.38 (t, 2 H), 4.03 (s, 2 H), 4.23 (t, 2 H), 4.29 (s, 4 H), 4.58 (d, 2 H), 7.20-7.29 (m, 5 H), 7.45 (d, 1 H), 7.50 (s, 1 H), 8.08 (s, 1 H), 8.64 (s, 1 H), 8.89 (s, 1 H), 9.15 (t, 1 H), 11.38 (s, 1 H).

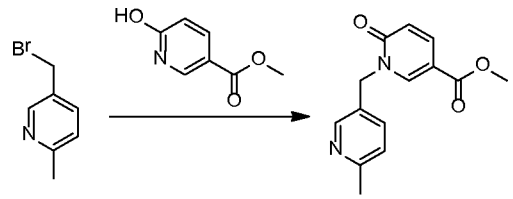
Example 160: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo- 1-((6-((2-oxopyrazin-1(2 H)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide



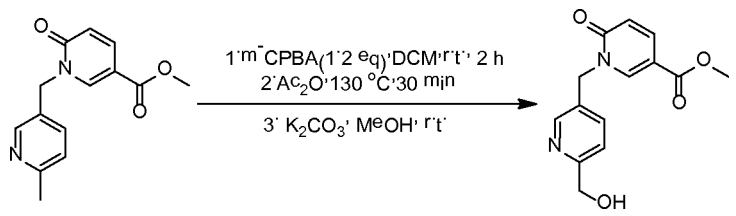
N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyrazin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide



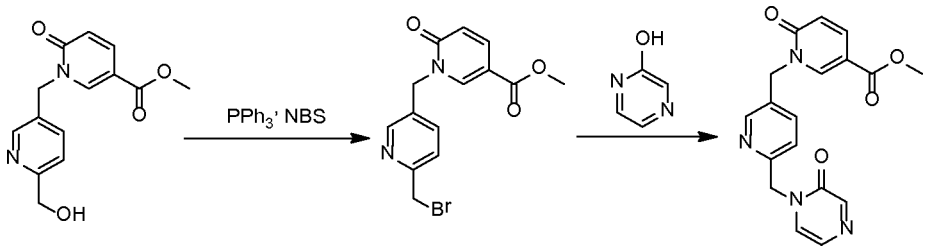
To a mixture of (6-methyl-pyridin-3-yl)-methanol (11.0 g, 89.32 mmol, 1.0 eq) in DCM (250 mL) was added PPh_3 (35.1 g, 133.98 mmol, 1.5 eq) at 0 °C followed by NBS (17.5 g, 98.25 mmol, 1.1 eq). The resultant mixture kept stirring for 1 h. The reaction mixture was concentrated to 50 mL. Crude 5-bromomethyl-2-methyl-pyridine was used directly for the next step without further purification.



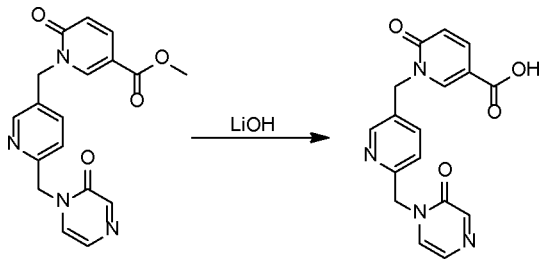
To a solution of 6-hydroxy-nicotinic acid methyl ester (13.6 g, 89.32 mmol, 1.0 eq) in DMF (150 mL) was added K_2CO_3 (24.7 g, 178.64 mmol, 2 eq).The reaction mixture was stirred for 30 min, and then crude 5-bromomethyl-2-methyl-pyridine was added. The resultant mixture was stirred overnight. Water (300 mL) was added, and the mixture was extracted with DCM. The organic phase was washed with brine and water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column (EA) to give 1-(6-methyl-pyridin-3-ylmethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (10 g, 43%) as a yellow oil.



To a solution of 1-(6-methyl-pyridin-3-ylmethyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (10.0 g, 38.72 mmol, 1.0 eq) in DCM (100mL) was added *m*-CPBA (8.0 g, 46.46 mmol, 1.2 eq).The resultant mixture was stirred for 2 h. And then sat.$NaHCO_3$ was added and the organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in Ac_2O (50 mL), and the resultant mixture was heated to 130 °C and kept stirring for 30 min. The solvent was removed in vacuo. Sat. $NaHCO_3$ was added, and the mixture was extracted with DCM. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in MeOH, and K_2CO_3 (10.7 g, 77.44 mmol, 2.0 eq) was added, and kept stirring for 2 h. The reaction mixture was concentrated. The residue was purified by column (DCM/ MeOH = 30/ 1) to give 1-(6-hydroxymethyl-pyridin-3-yl methyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (1.8 g, 19%) as a white solid.

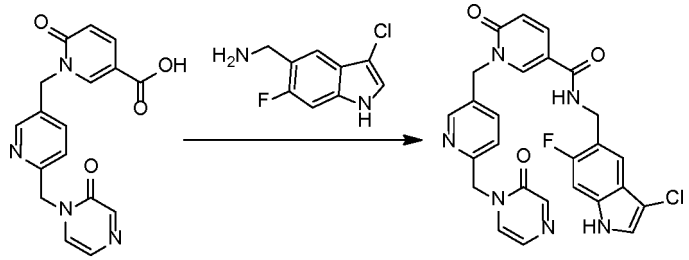


To a solution of 1-(6-hydroxymethyl-pyridin-3-ylmethyl)-6-oxo-1,6-dihydro-pyridine-3- carboxylic acid methyl ester (1.0 mg, 3.65 mmol,1.0 eq) in DCM (50 mL) was added PPh_3 (1.1 g, 4.38 mmol, 1.2 eq) followed by NBS (0.65 g, 3.65 mmol, 1.0 eq) in portions at 0 °C. The reaction mixture was kept stirring for 2 h. The reaction mixture was concentrated to 8 mL and the slurry was added to the solution of Pyrazin-2-ol (351 mg, 3.65 mmol, 1.0 eq) and K_2CO_3 (1.5 g, 10.95 mmol, 3.0 eq) in DMF (30 mL). The resultant mixture was stirred for 2 h. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (DCM/ MeOH = 30/ 1) to give 6-oxo-1-[6-(2-oxo-2 H-pyrazin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6-dihydro-pyridine-3- carboxylic acid methyl ester (1.0 g, 77%) as a white solid.



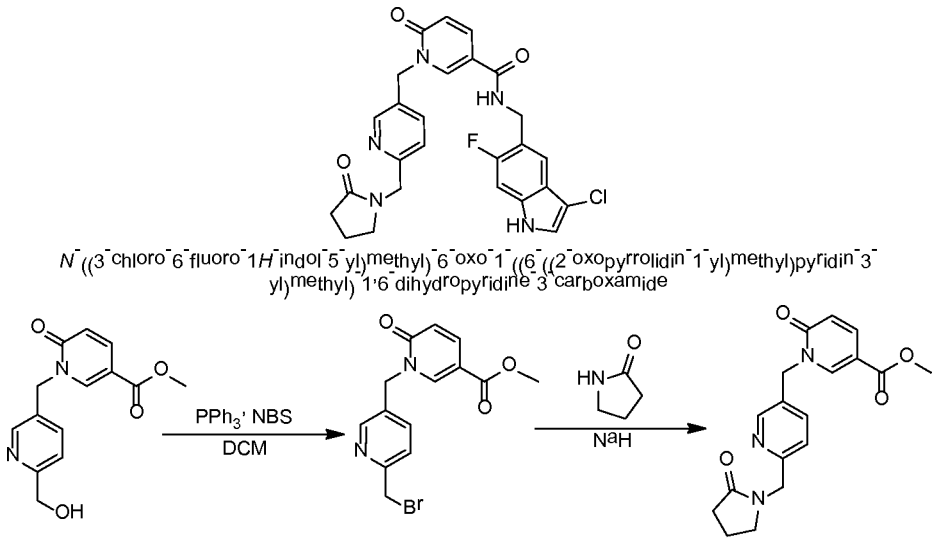
To a solution of 6-oxo-1-[6-(2-oxo-2 H-pyrazin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6- dihydro-pyridine-3-carboxylic acid methyl ester (1.0 g, 2.84 mmol, 1.0 eq) in THF/water (10 mL/10 mL) was added $LiOH.H_2O$ (179 mg, 4.26 mmol, 1.5 eq) and then the reaction mixture was kept stirring for 2 h. The reaction mixture was

concentrated to give 6-oxo-1-[6-(2-oxo-2 H-pyrazin-1- ylmethyl)-pyridin-3-ylmethyl]-1,6-dihydro-pyridine-3-carboxylic acid (1.2 g) as a brown solid.



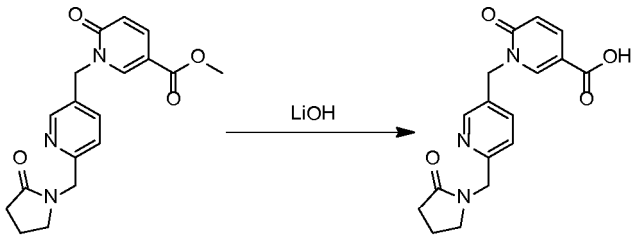
To a solution of 6-oxo-1-[6-(2-oxo-2 H-pyrazin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6- dihydro-pyridine-3-carboxylic acid (100 mg, 0.29 mmol, 1.0 eq) in DMSO (10 mL) was added C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (68 mg, 0.29 mmol, 1.0 eq) followed by EDCI (67 mg, 0.35 mmol, 1.2 eq), HOBT (47 mg, 0.35 mmol, 1.2 eq) and TEA (88 mg, 0.87 mmol, 3.0 eq). The reaction mixture was heated to 30 °C and kept stirring for overnight. LRMS showed SM was consumed. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (DCM/ MeOH = 10/ 1) to give N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyrazin-1(2 H)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide (25 mg, 17%) as a white solid. LRMS ($M+H^+$) m/z calculated 519.1, found/ 519.1; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.53 (d, 2 H), 5.15 (s, 4 H), 6.44 (d, 1 H), 7.21 (d, 1 H), 7.31-7.36 (m, 2 H), 7.44 (d, 1 H), 7.50 (s, 1 H), 7.71-7.74 (m, 2 H), 7.92 (d, 1 H), 8.00 (s, 1 H), 8.50 (s, 1 H), 8.55 (s, 1 H), 8.75(t, 1 H), 11.39 (s, 1 H);.

Example 161: Preparation of N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-6-oxo- 1-((6-((2-oxopyrrolidin-1-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide

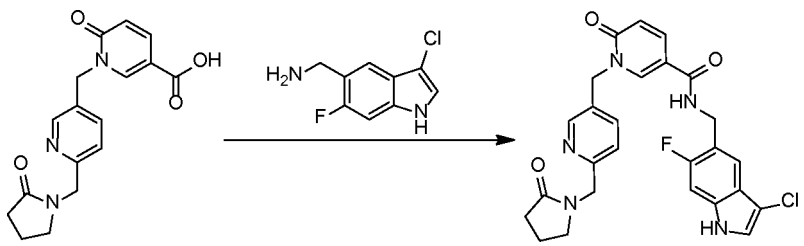


To a solution of 1-(6-hydroxymethyl-pyridin-3-ylmethyl)-6-oxo-1,6-dihydro-pyridine-3- carboxylic acid methyl ester (1.0 mg, 3.65 mmol, 1.0 eq) in DCM (50 mL) was added PPh_3 (1.1 g, 4.38 mmol, 1.2 eq) followed by NBS (0.65 g, 3.65mmol, 1.0 eq) in portions at 0 °C. The reaction mixture was kept stirring for 2 h. LRMS showed the SM was consumed. The reaction mixture was concentrated to 8 mL and the residue was purified by column to give the crude intermediate bromide. It was added to the solution of pyrrolidin-2-one

(310 mg, 3.65 mmol, 1.0 eq) and NaH (60%, 0.73 g, 10.95 mmol, 3.0 eq) in DMF (30 mL). The resultant mixture was stirred for 2 h. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (DCM/ MeOH = 30/ 1) to give 6-oxo-1-[6-(2-oxo-pyrrolidin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6-dihydro-pyridine-3- carboxylic acid methyl ester (0.5g, 42%) as a white solid.

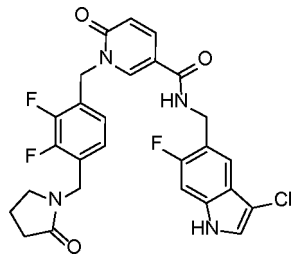


To a solution of 6-oxo-1-[6-(2-oxo-pyrrolidin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6- dihydro-pyridine-3-carboxylic acid methyl ester (0.5 g, 1.46 mmol, 1.0 eq) in THF/water (5 mL/5mL) was added LiOH.H_2O (92 mg, 2.2 mmol, 1.5 eq) and then the reaction mixture was kept stirring for 2 h. The reaction mixture was concentrated to give the crude 6-Oxo-1-[6-(2-oxo-pyrrolidin-1-ylmethyl) -pyridin-3-ylmethyl]-1,6-dihydro-pyridine-3-carboxylic acid (0.7g) as a brown solid.

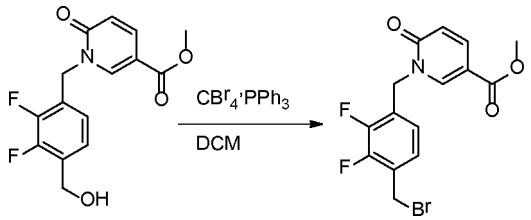


To a solution of 6-oxo-1-[6-(2-oxo-pyrrolidin-1-ylmethyl) -pyridin-3-ylmethyl]-1,6- dihydro-pyridine-3-carboxylic acid (100 mg, 0.31 mmol, 1.0 eq) in DMSO (10 mL) was added compound C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (73 mg, 0.31 mmol, 1.0 eq) followed by EDCI (70 mg, 0.37 mmol, 1.2 eq), HOBT (50 mg, 0.37 mmol, 1.2 eq) and TEA (94 mg, 0.93 mmol, 3.0 eq). The reaction mixture was heated to 30 °C and kept stirring for overnight. LCMS showed the SM was consumed. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyrrolidin-1-yl)methyl)pyridin-3- yl)methyl)-1,6-dihydropyridine-3-carboxamide (20 mg, 13%) as a white solid. LRMS ($M+H^+$) m/z calculated 508.1, found 508.1; ^{1}H NMR (CD_3OD, 400 MHz) δ 2.07 (m, 2 H), 2.46 (t, 2 H), 3.43 (t, 2 H), 4.57 (s, 2 H), 4.68 (s, 2 H), 5.26 (s, 2 H), 6.58 (d, 1 H), 7.14 (d, 1 H), 7.25 (s, 1 H) , 7.32 (d, 1 H), 7.52 (d, 1 H), 7.83 (d, 1 H), 8.99(d, 1 H), 8.47 (s, 1 H) , 8.57 (s, 1 H).

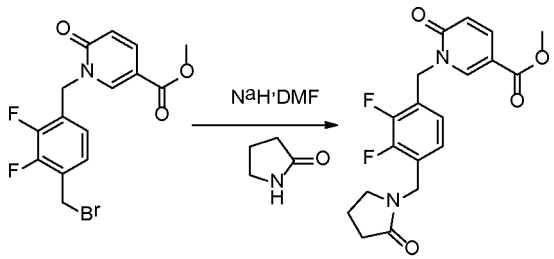
Example 162: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(2,3-difluoro- 4-((2-oxopyrrolidin-1-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



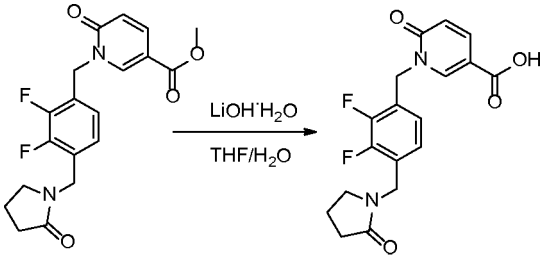
N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrrolidin-1-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



To a solution of 1-(2,3-difluoro-4-hydroxymethyl-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (1.2 g, 3.88 mmol, 1.0 eq) in DCM (20 mL) was added PPh_3 (1.22 g, 4.66 mmol, 1.2 eq) and CBr_4 (1.55 g, 4.66 mmol, 1.2 eq). The mixture was stirred at rt for 12 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 3/1-1/1) to afford 1-(4-bromomethyl-2,3-difluoro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester as a white solid (400 mg, 29%).

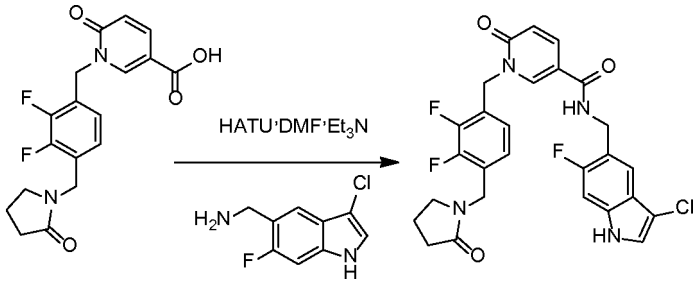


To a solution of 1-(4-bromomethyl-2,3-difluoro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (100 mg, 0.27 mmol, 1.0 eq) in DMF (10 mL) was added NaH (30 mg, 1.35 mmol, 5.0 eq) and 2-pyrrolidone (26 mg, 0.3 mmol, 1.1 eq) . The mixture was stirred at rt for 2 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 3/1-1/1) to afford 1-[2,3-difluoro-4-(2-oxo-pyrrolidin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester as a white solid (80 mg, 79%).



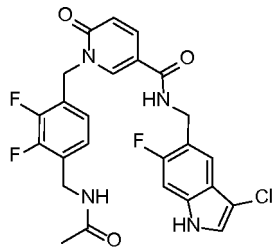
The mixture of 1-[2,3-difluoro-4-(2-oxo-pyrrolidin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (80 mg, 0.21 mmol, 1.0 eq) and $LiOH \cdot H_2O$ (18 mg, 0.43 mmol, 2.0 eq) in THF

(5 mL) and water (1 mL) was stirred at rt for 2 h. The reaction mixture was acidified to pH 3 by HCl (1 N), and extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product 1-[2,3-difluoro-4-(2-oxo-pyrrolidin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (80 mg, quant).

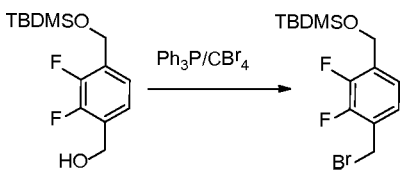


To a solution of 1-[2,3-difluoro-4-(2-oxo-pyrrolidin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (80 mg, 0.21 mmol, 1.0 eq) in DMF (5 mL) was added C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (50 mg, 0.21 mmol, 1.0 eq) followed by HATU (96 mg, 0.25 mmol, 1.2 eq) and TEA (106 mg, 1.05 mmol, 5.0 eq). The reaction mixture was stirred overnight at room temperature. LCMS showed the SM was consumed. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give the desired product N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrrolidin-1-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (20 mg) as a white solid. LRMS ($M+H^+$) m/z calculated 543.1, found 543.1. ^1H NMR (CD_3OD, 400 MHz): δ 1.89-1.94 (m, 2 H), 2.29 (t, 2 H), 3.24 (t, 2 H), 4.41 (s, 2 H), 4.55 (s,1 H), 5.16 (s, 2 H), 6.44 (d, 1 H), 6.94 (m, 2 H), 7.02 (d, 1 H), 7.12(s,1 H) , 7.39 (d, 1 H), 7.87 (d, 1 H), 8.28 (s, 1 H).

Example 163: Preparation of 1-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6- fluoro-1H -indol-5-yl)methyl)-1,6-dihydro-6-oxopyridine-3-carboxamide

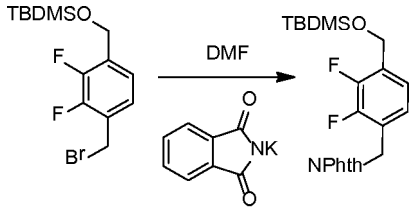


1-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

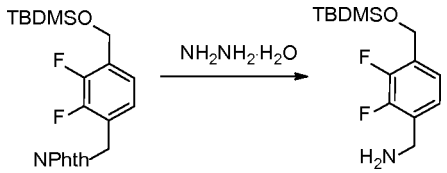


To a solution of [4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-phenyl]-methanol (10.0 g, 34.7 mmol, 1.0 eq) in DCM (100 mL) was added the PPh_3 (10.1 g, 38.2 mmol, 1.1 eq) and CBr_4 (12.7 g, 38.2 mmol, 1.1 eq). The reaction mixture was stirred for 2 h at rt Water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject

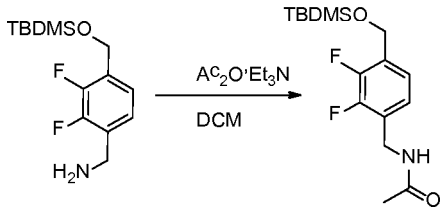
to silica gel chromatography (PE/ EA = 10/ 1-5/ 1) to afford (4-bromomethyl-2,3-difluoro-benzyloxy)-*tert*-butyl-dimethyl-silane as a white solid (4.1 g, 34%).



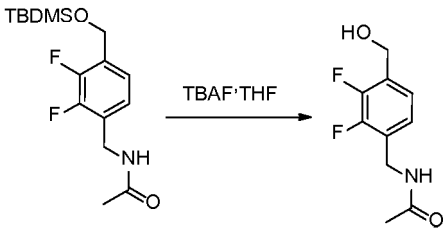
To a solution of (4-bromomethyl-2,3-difluoro-benzyloxy)-*tert*-butyl-dimethyl-silane (4.1 g, 11.4 mmol, 1.0 eq) in DMF (50 mL) under N_2, potassium phthalimide (17.5 g, 94 mmol, 1.5 eq) was added and the resulting mixture was at rt for 2 h. The mixture was poured into water and extracted with EtOAc (200 mL X 2). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was subject to silica gel chromatography (PE/ EA = 10/ 1-5/ 1) to afford 2-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-benzyl]-isoindole-1,3-dione as a white solid (3.6 g, 75.7%).



To a solution of 2-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-benzyl]-isoindole-1,3-dione (3.6 g, 8.6 mmol, 1.0 eq) in EtOH (50 mL) was added the $N_2H_4.H_2O$ (2.2 g, 43.2 mmol, 5.0 eq). The reaction mixture was stirred for 1 h at rt Water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-benzylamine was used without further purification (2.8 g, quant).

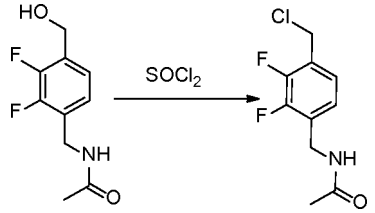


To a solution of 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-benzylamine (2.8 g, 10.0 mmol, 1.0 eq) in DCM (50 mL) was added the Ac_2O (2.1 g, 20.0 mmol, 2.0 eq) and Et_3N (2.1 g, 20 mmol, 2.0 eq). The reaction mixture was stirred for 1 h at rt Water was added, and the mixture was extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 5/ 1 - 2/ 1) to afford N-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-benzyl]-acetamide as a white solid (2.95 g, 90%).

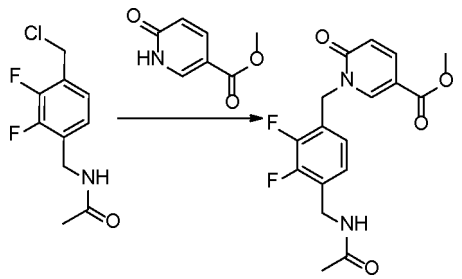


To a solution of N-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,3-difluoro-benzyl]-acetamide (2.95 g, 9.0 mmol, 1.0 eq) in THF (40 mL) was added the TBAF (4.2 g, 13.5 mmol, 1.5 eq). The reaction mixture was

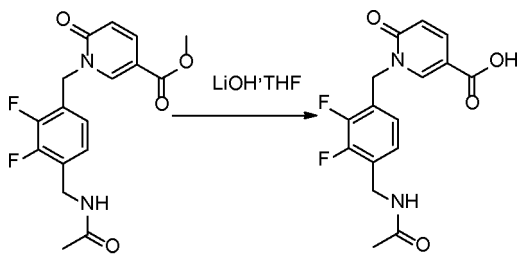
stirred for 3 h at rt The solvent was removed, and water was added. Then the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 5/ 1 - 2/ 1) to afford N-(2,3-difluoro-4-hydroxymethyl-benzyl)-acetamide as a off-white solid (1.1 g, 56.8%).



To a solution of N-(2,3-difluoro-4-hydroxymethyl-benzyl)-acetamide (0.6 g, 2.8 mmol, 1.0 eq) in $CHCl_3$ (20 mL) was added the $SOCl_2$ (0.5 g, 4.2 mmol, 1.5 eq). The reaction mixture was stirred for 3 h at 80 °C. The solvent was removed, and water was added. Then the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 10/ 1 - 5/ 1) to afford N-(4-chloromethyl-2,3-difluoro-benzyl)-acetamide as a off-white solid (0.5 g, 76.6%).

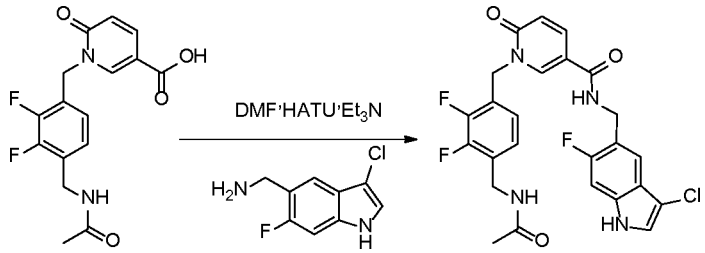


To a solution of N-(4-chloromethyl-2,3-difluoro-benzyl)-acetamide (150 mg, 0.64 mmol, 1.0 eq) in DMF (5 mL) was added the K_2CO_3 (177 mg, 1.28 mmol, 2.0 eq) and 6-hydroxy-nicotinic acid methyl ester (117 mg, 0.77 mmol, 1.2 eq). The reaction mixture was stirred for 3 h at 35 °C. Water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 3/ 1 - 1/ 1) to afford 1-[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester as an off-white solid (220 mg, 99%). ^1H NMR (DMSO-d_6, 400 MHz) δ 1.84 (s, 3 H), 3.80 (s, 3 H), 4.26 (d, 2 H), 6.45 (d, 1 H), 6.97 (t, 1 H), 7.08 (t, 1 H), 7.83 (d, 1 H), 8.36 (t, 1 H), 8.65 (s, 1 H).



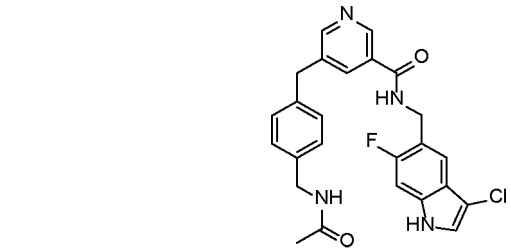
To a solution of 1-[4-(aetylamino-methyl)-2,3-difluoro-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (220 mg, 0.63 mmol, 1.0 eq) in THF (5 mL) and H_2O (1 mL) was added the $LiOH•H_2O$ (30 mg, 0.7 mmol, 1.1 eq). The reaction mixture was stirred for 1 h at 35 °C. Water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product 1-

[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid was used without further purification as an off-white solid (200 mg, 96%).

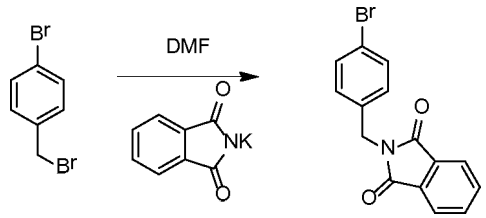


To a solution of 1-[4-(acetylamino-methyl)-2,3-difluoro-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (80 mg, 0.234 mmol, 1.0 eq) in DMF (5 mL) was added C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (50 mg, 0.213 mmol, 1.0 eq) followed by HATU (97 mg, 0.26 mmol, 1.2 eq) and TEA (108 mg, 1.07 mmol, 5.0 eq). The reaction mixture was stirred overnight at room temperature. LCMS showed the SM was consumed. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give 1-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-1,6-dihydro-6-oxopyridine-3-carboxamide (60 mg) as a white solid. LRMS ($M+H^+$) m/z calculated 517.1, found 517.1; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.83 (s, 3 H), 4.26 (d, 2 H), 4.54 (d, 2 H), 5.20 (s, 2 H), 6.45 (d, 1 H), 6.96 (t, 1 H),7.08 (d, 1 H), 7.22 (d, 1 H), 7.45 (d, 1 H), 7.50 (d, 1 H), 7.94-7.97 (m, 1 H), 8.35 (t, 1 H), 8.47 (s, 1 H), 8.76 (t, 1 H), 11.38 (s, 1 H).

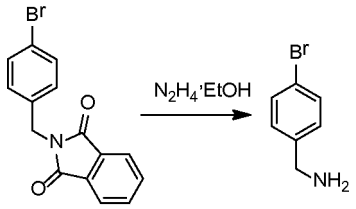
Example 164: Preparation of 5-(4-(acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)pyridine-3-carboxamide



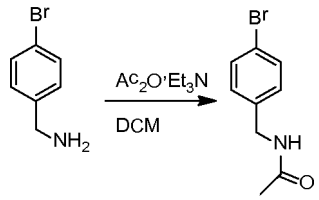
5-(4-(acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide



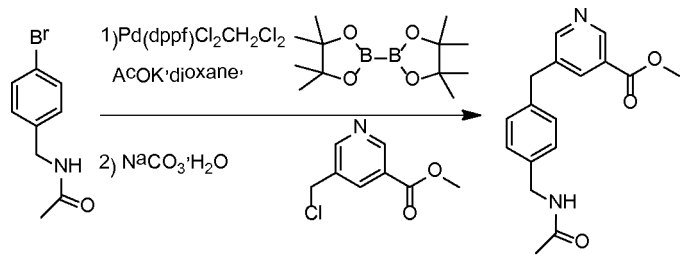
To a solution of 1-bromo-4-bromomethyl-benzene (3.0 g, 12.0 mmol, 1.0 eq) in DMF (40 mL) was added phthalimide potassium (4.4 g, 24.0 mmol, 2.0 eq). The reaction mixture was stirred for 1 h at rt Water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give 2-(4-bromo-benzyl)-isoindole-1,3-dione which was used as a white solid (4.0 g, quant)without further purification.



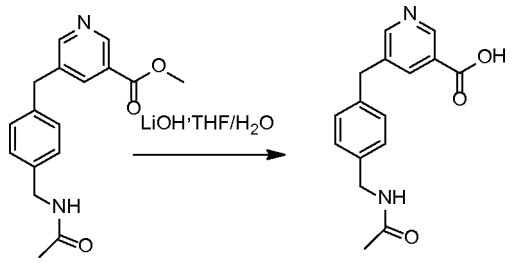
To a solution of 2-(4-bromo-benzyl)-isoindole-1,3-dione (4.1 g, 13.1 mmol, 1.0 eq) in EtOH (50 mL) was added the $N_{2\,H4}\cdot H_2O$ (3.3 g, 65.5 mmol, 5.0 eq). The reaction mixture was stirred for 1 h at rt The solvent was evaporated and water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give 4-bromo-benzylamine which was used without purified as a white solid (2.83 g, quant).



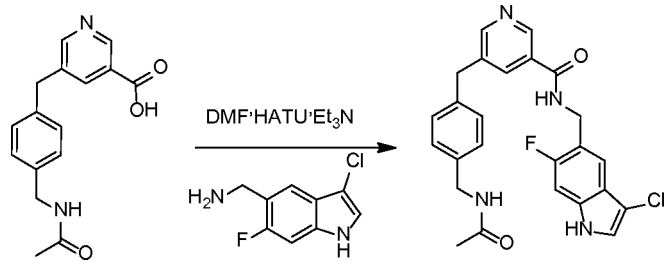
To a solution of 4-bromo-benzylamine (2.83 g, 15.3 mmol, 1.0 eq) in DCM (50 mL) was added the Ac_2O (2.34 g, 23.0 mmol, 1.5 eq) and Et_3N (2.34 g, 23.0 mmol, 1.5 eq). The reaction mixture was stirred for 1 h at rt The solvent was evaporated, and water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 5/ 1 - 2/ 1) to afford N-(4-bromo-benzyl)-acetamide as a white solid (1.5 g, 43%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.86 (s, 3 H), 4.21 (d, 2 H), 7.20 (d, 2 H), 7.50 (d, 2 H), 8.36 (s, 1 H).



To a solution of N-(4-bromo-benzyl)-acetamide (1.5 g, 6.6 mmol, 1.0 eq) in dioxane (40 mL) was added 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (1.7 g, 6.6 mmol,1.0 eq), $Pd(dppf)Cl_2CH_2Cl_2$ (0.29 g, 0.66 mmol, 0.1 eq) and AcOK (1.94 g, 19.8 mmol, 3.0 eq). The mixture was stirred at 80 °C for 12 h and allowed to cool to rt Then to this mixture was added 5-chloromethyl-nicotinic acid methyl ester (1.47 g, 6.6 mmol, 1.0 eq), $NaCO_3$ (2.12 g, 0.19.8 mmol, 3.0 eq) and H_2O (8 mL). The mixture was stirred at 95 °C for 2 h and allowed cool to rt The reaction mixture was extracted with EtOAc (100 mL×3). The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 5/ 1 - 2/ 1) to afford 5-[4-(acetylamino-methyl)-benzyl]-nicotinic acid methyl ester as a yellow solid (1.2 g, 61%).^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.84 (s, 3 H), 3.86 (s, 3 H), 4.04 (s, 2 H), 4.19 (d, 2 H), 7.17-7.25 (m, 4H), 8.09 (t, 2 H), 8.30 (s, 1 H), 8.75 (d, 2 H), 8.91 (d, 2 H).

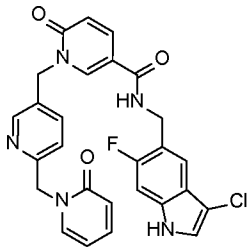


To a solution of 5-[4-(acetylamino-methyl)-benzyl]-nicotinic acid methyl ester (100 mg, 0.34 mmol, 1.0 eq) in THF (5 mL) and H_2O (1 mL) was added the LiOH.H_2O (22 mg, 0.51 mmol, 1.5 eq). The reaction mixture was stirred for 1 h at 35 °C. Water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give 5-[4-(acetylamino-methyl)-benzyl]-nicotinic acid was used without purification as a yellow oil (95 mg, 99%).

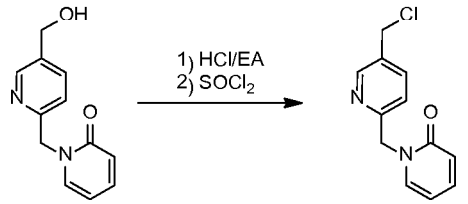


To a solution of 5-[4-(acetylamino-methyl)-benzyl]-nicotinic acid (95 mg, 0.34 mmol, 1.0 eq) in DMF (5 mL) was added C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (70 mg, 0.31 mmol, 0.9 eq) followed by HATU (155 mg, 0.41 mmol, 1.2 eq) and TEA (172 mg, 1.7 mmol, 5.0 eq). The reaction mixture was stirred overnight at rt. LCMS showed the SM was consumed. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give 5-(4-(acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)pyridine-3-carboxamide (65 mg, 46%) as a white solid. LRMS ($M+H^+$) m/z calculated 465.1, found 465.1; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.83 (s, 3 H), 4.00 (s, 2 H), 4.19 (d, 2 H), 4.58 (d, 2 H), 7.17-7.23 (m,5H), 7.45 (d, 2 H), 7.50 (d, 2 H), 8.05 (s, 1 H), 8.26 (t, 2 H), 8.53 (s, 1 H), 8.88 (s, 1 H), 9.15 (t, 2 H), 11.39 (s, 1 H).

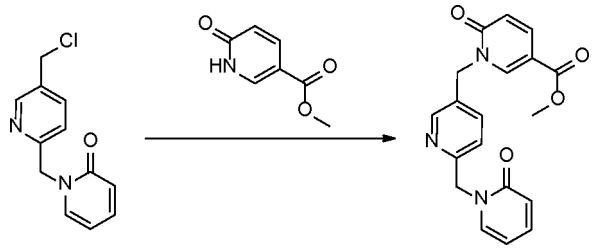
Example 165: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyridin -1(2 H)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide



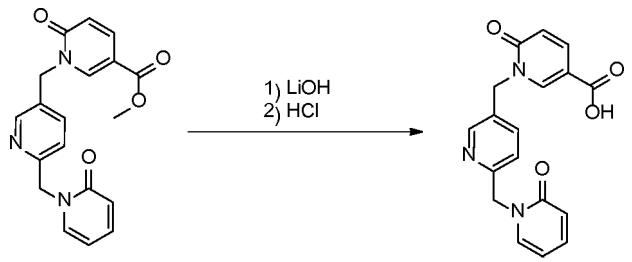
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide



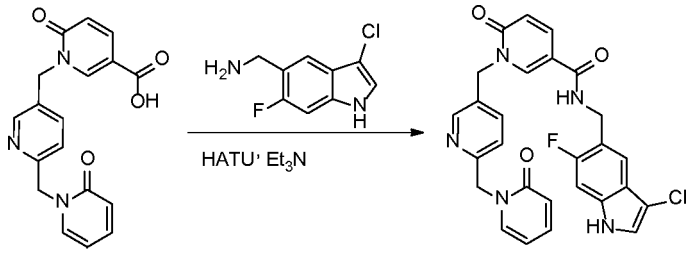
To a solution of [6-(tetrahydro-furan-2-yl)-pyridin-3-yl]-methanol (1.6 g, 7.40 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 0.5 h and the excess reagent was removed by evaporation. The residue was treated with $SOCl_2$ (18 mL) and the mixture was heated under reflux for 1 h. The excess reagent was removed in vacuo to give 1-(5-chloromethyl-pyridin-2-ylmethyl)-1 H-pyridin-2-one as a yellow solid (1.92 g, 96%).



To a solution of 1-(5-chloromethyl-pyridin-2-ylmethyl)-1 H-pyridin-2-one (500 mg, 1.85 mmol, 1 eq) and 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (284 mg, 1.85 mmol, 1 eq) in acetone (20 mL) was added K_2CO_3 (1.28 g, 9.25 mmol, 5 eq). The mixture was stirred under reflux for 24 h and the solvent was removed in vacuo. The residue was diluted with water and extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (EA) to give 6-oxo-1-[6-(2-oxo-2 H-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6-dihydro-pyridine-3-carboxylic acid methyl ester as an off-white solid (100 mg, 15%).

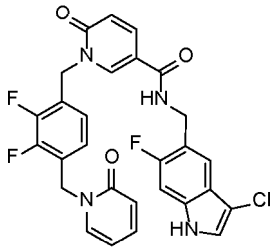


To a solution of 6-oxo-1-[6-(2-oxo-2H-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (100 mg, 0.284 mmol, 1.0 eq) in THF (5 mL)/ H_2O (1 mL) was added $LiOH.H_2O$ (14 mg, 0.342 mmol, 1.2 eq). The mixture was stirred at 40 °C for 30 min and was acidified to pH 5 with 1N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification.

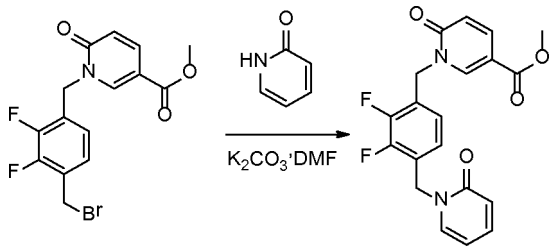


To a solution of the above crude product and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (67 mg, 0.284 mmol, 1 eq) in DCM (4 mL) was added HATU (130 mg, 0.342 mmol, 1.2 eq) and Et_3N (0.16 mL, 1.136 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/ MeOH = 10/ 1) to give N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyridin-1(2 H)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide as a white solid (32 mg, 22% yields for 2 steps). LRMS ($M+H^+$) m/z calculated 518.1, found 518.1; ^1H NMR (CD_3OD, 400 MHz): 8.32 (s, 1 H), 8.20 (s, 1 H), 7.72 (d, 1 H), 7.56-7.50 (m, 2 H), 7.33-7.27 (m, 2 H), 7.07-7.00 (m, 2 H), 6.89 (d, 1 H), 6.34-6.30 (m, 2 H), 6.18 (t, 1 H), 5.02 (s, 2 H), 4.99 (s, 2 H), 4.23 (s, 2 H).

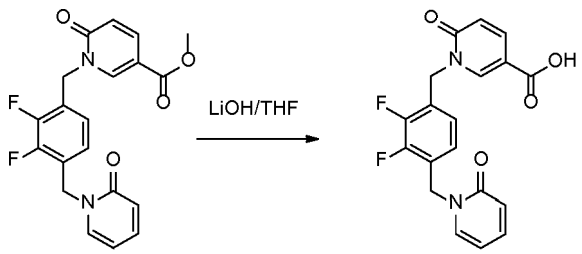
Example 166: Preparation of N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-1-(2,3-difluoro -4- ((2-oxopyridin-1(2 H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

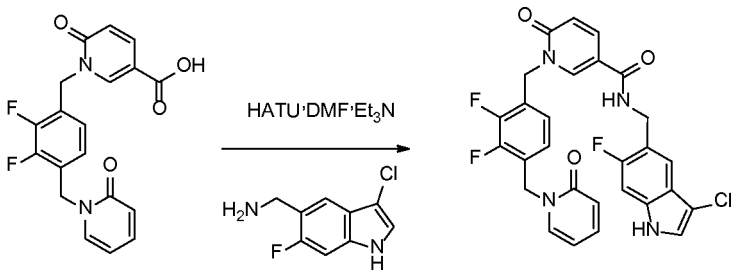


To a solution of 1-(4-bromomethyl-2,3-difluoro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (160 mg, 0.43 mmol, 1.0 eq) in DMF (10 mL) was added K_2CO_3 (82 mg, 0.87 mmol, 2.0 eq) and pyridin-2-ol (72 mg, 0.52 mmol, 1.2 eq) . The mixture was stirred at rt for 3 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/ EA = 3/ 1 - 1/ 1) to afford 1-[2,3-difluoro-4-(2-oxo-2 H-pyridin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester as a white solid (110 mg, 66%).



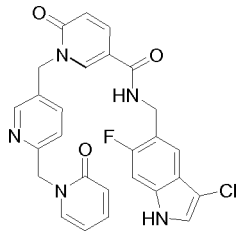
The mixture of 11-[2,3-difluoro-4-(2-oxo-2 H-pyridin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (110 mg, 0.285 mmol, 1.0 eq) and $LiOH{\cdot}H_2O$ (18 mg, 0.43 mmol, 1.5 eq) in THF

(5 mL) and water (1 mL) was stirred at rt for 2 h. The reaction mixture was acidified to pH 3 by HCl (1N), and extracted with ethyl acetate. The organic layer was washed with brine and water, dried over Na_2SO_4 and evaporated to give the crude product 1-[2,3-difluoro-4-(2-oxo-2 H-pyridin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (100 mg, quant).

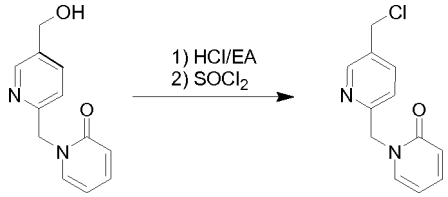


To a solution of 1-[2,3-difluoro-4-(2-oxo-2 H-pyridin-1-ylmethyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (100 mg, 0.27 mmol, 1.0 eq) in DMF (5 mL) was added C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (70 mg, 0.30 mmol, 1.1 eq) followed by HATU (125 mg, 0.33 mmol, 1.2 eq) and TEA (164 mg, 1.62 mmol, 6.0 eq). The reaction mixture was stirred overnight at rt. LCMS showed the SM was consumed. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give the desired product N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyridin-1(2 H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide as a white solid (45 mg, 30%). LRMS (M+H+) m/z calculated 553.1, found 553.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.54 (d, 2 H), 5.13 (s, 2 H), 5.20 (s, 2 H), 6.25 (t, 1 H), 6.38 (d,1 H), 6.43 (d, 1 H), 6.92 (m, 2 H), 7.20 (d, 1 H), 7.44 (m, 2 H), 7.50 (s,1 H) , 7.73 (d, 1 H), 7.95 (m, 1 H), 8.47 (s, 1 H), 8.74 (t, 1 H), 11.37 (s, 1 H).

Example 167: Preparation of N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyridin- 1(2 H)-yl) methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide

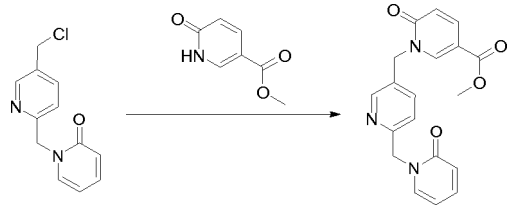


N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyridin-1(2H)-yl)methyl) pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide

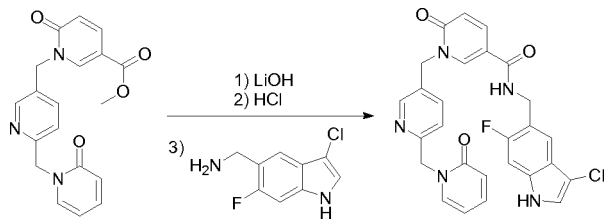


To a solution of [6-(tetrahydro-furan-2-yl)-pyridin-3-yl]-methanol (1.6 g, 7.40 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 0.5 h and the excess reagent was removed by evaporation. The residue was treated with $SOCl_2$ (18 mL) and the mixture was heated under reflux for 1 h. The excess

reagent was removed in vacuo to give 1-(5-chloromethyl-pyridin-2-ylmethyl)-1H-pyridin-2-one (1.92 g, 96%) as a yellow solid.

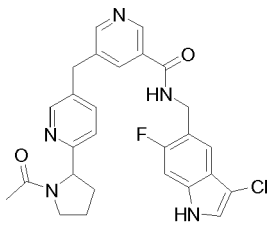


To a solution of 1-(5-chloromethyl-pyridin-2-ylmethyl)-1H-pyridin-2-one (500 mg, 1.85 mmol, 1 eq) and 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (284 mg, 1.85 mmol, 1 eq) in acetone (20 mL) was added K_2CO_3 (1.28 g, 9.25 mmol, 5 eq). The mixture was stirred under reflux for 24 h and the solvent was removed in vacuo. The residue was diluted with water and extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (EA) to give 6-oxo-1-[6-(2-oxo-2H-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (100 mg, 15%) as an off-white solid.

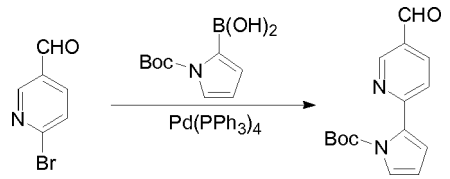


To a solution of 6-oxo-1-[6-(2-oxo-2 H-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (100 mg, 0.284 mmol, 1.0 eq) in THF (5 mL)/ H_2O (1 mL) was added $LiOH.H_2O$ (14 mg, 0.342 mmol, 1.2 eq). The mixture was stirred at 40 °C for 30 min and was acidified to pH 5 with 1N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification. To a solution of the above crude product and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (67 mg, 0.284 mmol, 1 eq) in DCM (4 mL) was added HATU (130 mg, 0.342 mmol, 1.2 eq) and Et_3N (0.16 mL, 1.136 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/MeOH = 10/ 1, v/v) to give N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide (32 mg, 22% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 517.1, found 517.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.32 (s, 1 H), 8.20 (s, 1 H), 7.72 (d, 1 H), 7.56-7.50 (m, 2 H), 7.33-7.27 (m, 2 H), 7.07-7.00 (m, 2 H), 6.89 (d, 1 H), 6.34-6.30 (m, 2 H), 6.18 (t, 1 H), 5.02 (s, 2 H), 4.99 (s, 2 H), 4.23 (s, 2 H).

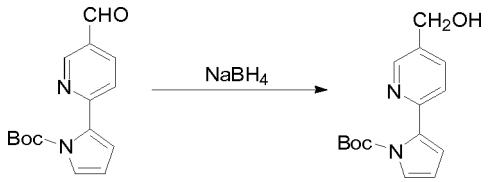
Example 168: Preparation of 5-((6-(1-acetylpyrrolidin-2-yl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)nicotinamide



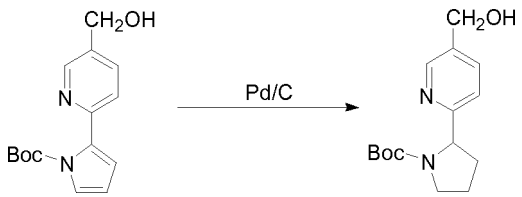
5-((6-(1-acetylpyrrolidin-2-yl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl) methyl)nicotinamide



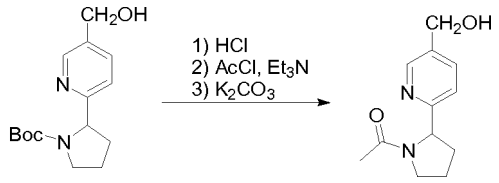
To a solution of 6-bromo-pyridine-3-carbaldehyde (4.4 g, 23.70 mmol, 1 eq) and N-Boc-2-pyrroleboronic acid (5.0 g, 23.70 mmol, 1 eq) in dioxane (160 mL) and water (40 mL) was added $Pd(PPh_3)_4$ (1.37 g, 1.19 mmol, 0.05 eq) and Na_2CO_3 (7.54 g, 71.10 mmol, 3 eq). The mixture was stirred at 95 °C for 2 h under nitrogen. The mixture was allowed to cool to rt. The solvent was removed in vacuo and the residue was diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (EA/PE = 1/ 5, v/v) to give 2-(5-formyl-pyridin-2-yl)-pyrrole-1-carboxylic acid *tert*-butyl ester (4.20 g, 66%) as a yellow solid.



To a solution of 2-(5-formyl-pyridin-2-yl)-pyrrole-1-carboxylic acid *tert*-butyl ester (2.2 g, 8.09 mmol, 1 eq) in MeOH (40 mL) was added $NaBH_4$ (615 mg, 16.18 mmol, 2 eq) portionwise at 0 °C. Then the mixture was stirred at rt for 1 h and diluted with saturated aqueous NH_4Cl solution. The combined mixture was concentrated to remove MeOH and resultant aqueous solution was extracted with DCM, dried and concentrated to give 2-(5-Hydroxymethyl-pyridin-2-yl)-pyrrole-1-carboxylic acid *tert*-butyl ester (2.2 g, quant).

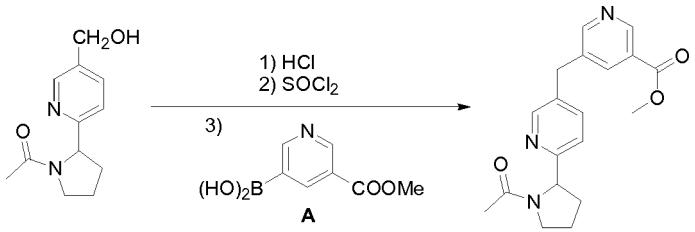


To a solution of 2-(5-Hydroxymethyl-pyridin-2-yl)-pyrrole-1-carboxylic acid *tert*-butyl ester (2.2 g, 8.09 mmol, 1 eq) in MeOH (40 mL) was added 10% Pd/C (600 mg). The mixture was stirred at 50 psi and 40 °C under H_2 for 30 h. Pd/C was removed by filtration and the filtrate was concentrated to give 2-(5-Hydroxymethyl-pyridin-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.0 g, 89%) as a yellow oil.

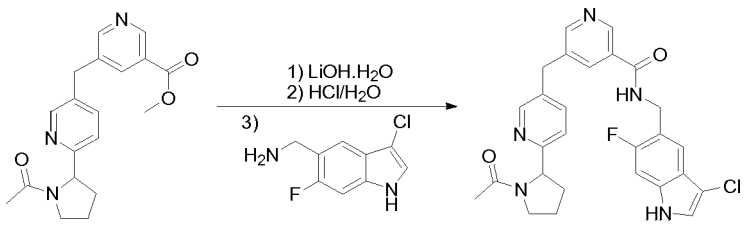


To a solution of 2-(5-Hydroxymethyl-pyridin-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (400 mg, 1.527 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 1 h and was concentrated in vacuo. The residue was re-dissolved in dry DCM (15 mL). To the solution was added AcCl (362 mg, 4.58 mmol, 3 eq) and Et_3N (0.73 mL, 6.108 mmol, 4 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with water. The organic layer was separated and washed with 1N HCl solution and brine. The mixture was dried and concentrated in vacuo.

To a solution of the above crude product in MeOH (15 mL) was added K_2CO_3 (421 mg, 3.054 mmol, 2 eq). The mixture was stirred at rt for 1 h and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column (EA/PE = 1/1, v/v) to give 1-[2-(5-Hydroxymethyl-pyridin-2-yl)-pyrrolidin-1-yl]-ethanone (240 mg, 71% for 3 steps) as a yellow oil.



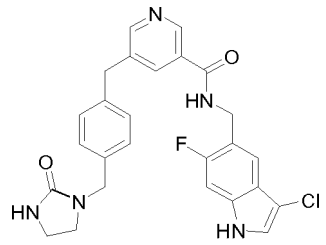
To a solution of 1-[2-(5-Hydroxymethyl-pyridin-2-yl)-pyrrolidin-1-yl]-ethanone (240 mg, 1.09 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 0.5 h and the excess reagent was removed by evaporation. The residue was treated with $SOCl_2$ (5 mL) and the mixture was heated under reflux for 1 h. The excess reagent was removed in vacuo. To a solution of the above residue and boroncic acid **A** (1.64 mmol, 1.5 eq) in dioxane (8.2 mL) and water (2.1 mL) was added Na_2CO_3 (462 mg, 4.36 mmol, 4 eq) and $(dppf)PdCl_2$ (44 mg, 0.055 mmol, 0.05 eq). The mixture was stirred at 90 °C for 1 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/MeOH = 20/1, v/v) to give 5-[6-(1-acetyl-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinic acid methyl ester (300 mg, 81% yields for 3 steps) as a brown oil.



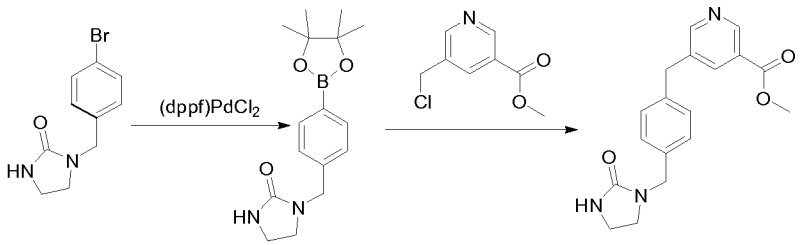
To a solution of 5-[6-(1-acetyl-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinic acid methyl ester (300 mg, 0.88 mmol, 1.0 eq) in THF (9 mL)/ H_2O (1 mL) was added $LiOH.H_2O$ (41 mg, 0.968 mmol, 1.1 eq). The mixture was stirred at 40 °C for 1 h and was acidified to pH 5 with 1N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification.

To a solution of the above crude product and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (207 mg, 0.88 mmol, 1 eq) in DCM (8 mL) was added HATU (401 mg, 1.056 mmol, 1.2 eq) and Et_3N (0.50 mL, 3.52 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/MeOH = 10/1, v/v) to give 5-((6-(1-acetylpyrrolidin-2-yl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)nicotinamide (300 mg, 67% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 506.1, found 506.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.77-8.76 (m, 1 H), 8.52-8.50 (m, 1 H), 8.36 (s, 0.35 H), 8.30 (s, 0.65 H), 8.00 (s, 1 H), 7.61-7.52 (m, 1 H), 7.41 (d, 1 H), 7.14-7.09 (m, 2 H), 7.02 (d, 1 H), 4.96-4.95 (m, 1 H), 4.59 (s, 2 H), 4.03 (s, 0.70 H), 4.00 (s, 1.30 H), 3.75-3.51 (m, 2 H), 2.34-2.19 (m, 1 H), 2.00 (s, 1.95 H), 1.91-1.77 (m, 3 H), 1.67 (s, 1.05 H).

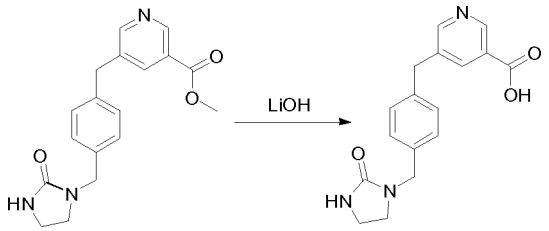
Example 169: Preparation of N-(3-Chloro-6-fluoro-1 H-indol-5-ylmethyl)-5-[4-(2-oxo-imidazolidin-1 -ylmethyl)-benzyl]-nicotinamide



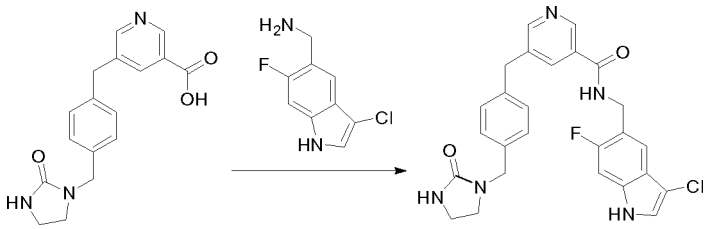
N-(3-Chloro-6-fluoro-1*H*-indol-5-ylmethyl)-5-[4-(2-oxo-imidazolidin-1-ylmethyl)-benzyl]-nicotinamide



To a solution of 1-(4-bromo-benzyl)-imidazolidin-2-one (0.7 g, 2.7 mmol, 1 eq) and $B_2(Pin)_2$ (0.84 g, 3.3 mmol, 1.2 eq) in dioxane (25 mL) was added KOAc (0.79g, 8.1mmol, 3 eq) and $(dppf)PdCl_2.CH_2Cl_2$ (110 mg, 0.11 mmol, 0.05 eq). The mixture was stirred at 95 °C under nitrogen for 2 h and cool down, to yield 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-imidazolidin-2-one as a crude compound. To a solution of compound 1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl) -benzyl]-imidazolidin-2-one and 5-chloromethyl-nicotinic acid methyl ester (0.6 g, 2.7 mmol, 1 eq) in dioxane (20 mL) and water (5 mL) was added Na_2CO_3 (0.86 g, 8.1 mmol, 3 eq), and $(dppf)PdCl_2.CH_2Cl_2$ (110 mg, 0.135 mmol, 0.05 eq). The mixture was stirred at 100 °C for 3 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/CH_3OH = 10/1, v/v) to give 5-[4-(2-oxo-imidazolidin-1-ylmethyl)-benzyl]-nicotinic acid methyl ester (0.82 g, 92%) as an orange solid.

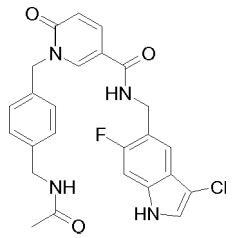


To a solution of compound 5-[4-(2-oxo-imidazolidin-1-ylmethyl)-benzyl]-nicotinic acid methyl ester (0.82 g, 2.5 mmol, 1 eq) in THF (90 mL) and water (10 mL) was added LiOH (0.138 g, 3.3 mmol, 1.3 eq). The mixture was stirred at 40 °C for 3 h and was acidified to pH 5~6 with 1N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification.

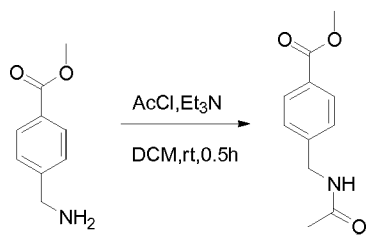


To a solution of compound 5-[4-(2-oxo-imidazolidin-1-ylmethyl)-benzyl]-nicotinic acid (100 mg, 0.3 mmol, 1 eq) and C-(3-chloro-6-fluoro-1 H-indol-5-yl) - methylamine (76 mg, 0.3 mmol, 1 eq) in DMF (4 mL) was added HOBT (52 mg, 0.386 mmol, 1.2 eq), EDCI (74 mg, 0.386 mmol, 1.2 eq) and Et_3N (0.13 g, 1.3 mmol, 4 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/CH_3OH = 10/1, v/v) to give N-(6-fluoro-1 H-indol-5-ylmethyl)-5-[4-(2-oxo-imidazolidin-1-ylmethyl)-benzyl]-nicotinamide (40 mg, 25.3% yield) as an off white solid. LRMS ($M+H^+$) m/z calculated 492.1, found 492.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.1 (t, 1 H), 8.9 (d, 1 H), 8.6 (d, 1 H), 8.1 (s, 1 H), 7.5 (s, 1 H), 7.46-7.44 (d, 1 H), 7.3-7.15 (m, 5H), 6.4 (s, 1 H), 4.6 (d, 2 H), 4.18 (s, 2 H), 4.02 (s, 2 H), 3.2-3.1 (m, 5 H).

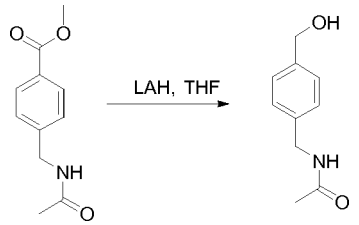
Example 170: Preparation of 1-(4-(acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl) methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



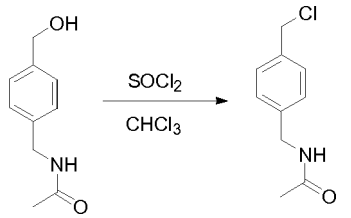
1-[4-(Acetylamino-methyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-amide



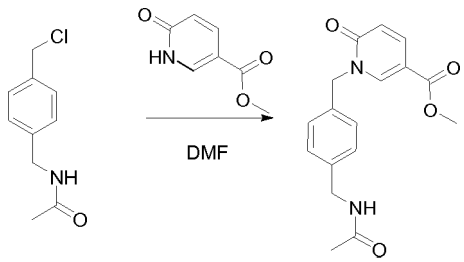
To a solution of 4-aminomethyl-benzoic acid methyl ester (3.0 g, 14.9 mmol, 1.0 eq) in DCM (50 mL) was added AcCl (1.76 g, 22.3 mmol, 1.5 eq) and Et_3N (4.51 g, 44.7 mmol, 3.0 eq) . The mixture was stirred at rt for 0.5 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to flash chromatography (PE/EA = 3/1 - 1/1, v/v) to afford 4-(acetylamino-methyl)-benzoic acid methyl ester as a white solid (2.95 g, 95.8%).



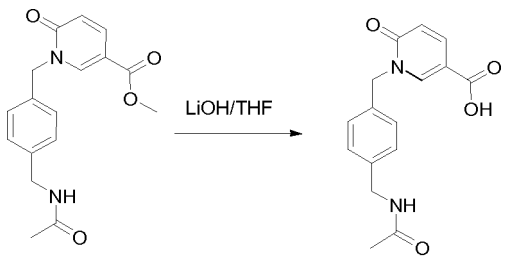
The mixture of 4-(acetylamino-methyl)-benzoic acid methyl ester (2.8 g, 13.5 mmol, 1.0 eq) and LAH (0.62 g, 16.2 mmol, 1.2 eq) in THF (50 mL) was stirred at rt for 1 h. The reaction was quenched with H_2O, and the reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to flash chromatography (PE/EA = 3/1 - 1/1, v/v) to afford *N*-(4-hydroxymethyl-benzyl)-acetamide as a yellow solid (0.6 g, 25.6%).



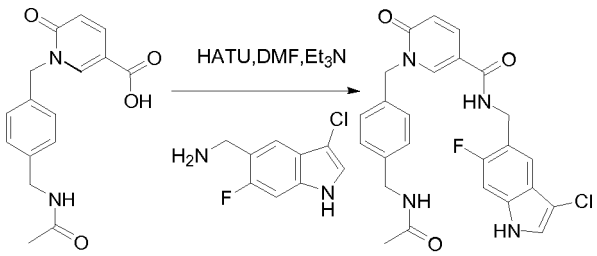
To a solution of *N*-(4-hydroxymethyl-benzyl)-acetamide (600 mg, 3.33 mmol, 1.0 eq) in $CHCl_3$ (30 mL) was added $SOCl_2$ (600 mg, 5.0 mmol, 1.5 eq). The reaction mixture was stirred for 1 h at 80 °C. LCMS showed the SM was consumed. The solvent was removed in vacuo. The residue was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and evaporated to give the crude product which was subject to flash chromatography (PE/EA = 5/1 - 2/1, v/v) to afford *N*-(4-chloromethyl-benzyl)-acetamide as a yellow solid (400 mg, 58%).



To a solution of *N*-(4-chloromethyl-benzyl)-acetamide (100 mg, 0.48 mmol, 1.0 eq) in DMF (5 mL) was added K_2CO_3 (133 mg, 0.96 mmol, 2.0 eq) and 6-hydroxy-nicotinic acid methyl ester (88 mg, 0.58 mmol, 1.2 eq). The mixture was stirred at rt for 3 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to flash chromatography (PE/EA = 3/1 - 1/1, v/v) to afford 1-[4-(acetylamino-methyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester as a white solid (80 mg, 53%).

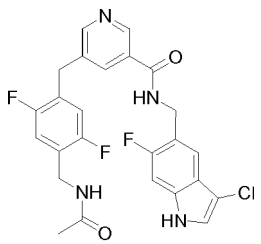


The mixture of 1-[4-(acetylamino-methyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester (80 mg, 0.255 mmol, 1.0 eq) and $LiOH \cdot H_2O$ (21 mg, 0.51 mmol, 2.0 eq) in THF (5 mL) and water (1 mL) was stirred at rt for 2 h. The reaction mixture was acidified to pH 3 by HCl (1 N), and extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product 1-[4-(acetylamino-methyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (70 mg, 93%).

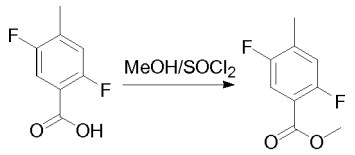


To a solution of -[4-(acetylamino-methyl)-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (70 mg, 0.255 mmol, 1.0 eq) in DMF (5 mL) was added C-(3-chloro-6-fluoro-1H-indol-5-yl)-methylamine (60 mg, 0.255 mmol, 1.0 eq) followed by HATU (116 mg, 0.306 mmol, 1.2 eq) and TEA (129 mg, 1.275 mmol, 5.0 eq). The reaction mixture was stirred overnight at room temperature. LCMS showed the SM was consumed. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give the desired product 1-[4-(acetylamino-methyl)-benzyl]-6-oxo- 1,6-dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1 H-indol-5-ylmethyl)-amide (10 mg) as a white solid. LRMS (M^+H^+) m/z calculated 481.1, found 481.1. ^1H NMR (CD_3OD, 400 MHz) δ 1.95 (s, 3 H), 4.31 (s, 2 H), 4.64 (s, 2 H),5.19 (s, 2 H), 4.55 (d,1 H), 7.10 (d, 1 H), 7.22 (s, 1 H), 7.25-7.31 (m, 4 H), 7.48 (d,1 H), 7.93-7.96 (m, 1 H) , 8.35 (s, 1 H).

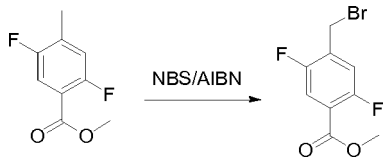
Example 171: 5-(4-(acetamidomethyl)-2,5-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5 -yl)methyl)nicotinamide



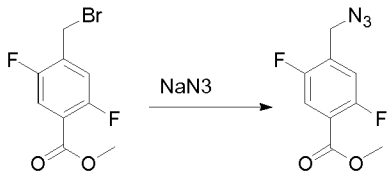
5-[4-(Acetylamino-methyl)-2,5-difluoro-benzyl]-*N*-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-nicotinamide



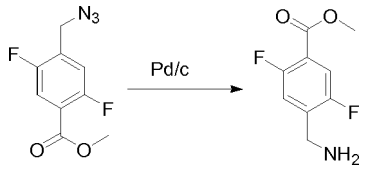
To a solution of 2,5-difluoro-4-methyl-benzoic acid (5 g, 29.0 mmol, 1.0 eq) in MeOH (200 mL) was added $SOCl_2$ (17.2 g, 145 mmol, 5 eq). The mixture was stirred at rt for 3 h and the excess reagent was removed in vacuo. The mixture was extracted with EA and purified by flash chromatography on silica gel column (PE/EA = 10/1, v/v) to give 2,5-difluoro-4-methyl-benzoic acid methyl ester (4.5 g, 83% yield) as colorless oil.



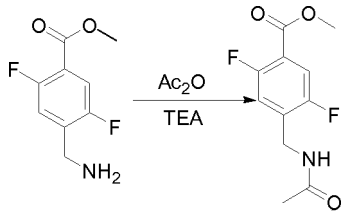
The mixture of 2,5-difluoro-4-methyl-benzoic acid methyl ester (4.0 g, 21.5mmol, 1.0 eq), NBS (4.0g, 22.5 mmol, 1.05 eq) and AIBN (0.088 g, 1.07 mmol, 0.05 eq) in CCl_4 (100 mL) was stirred at 80 °C overnight. The mixture was poured into water and extracted with CH_2Cl_2. The organic solution was dried and concentrated. The residue was purified by flash column chromatography on silica gel column (PE/EA = 10/1, v/v) to give 4-bromomethyl-2,5-difluoro-benzoic acid methyl ester (4 g, 70.1%) as a yellow solid.



To a solution of 4-bromomethyl-2,5-difluoro-benzoic acid methyl ester (4.0 g, 15.1 mmol, 1 eq) in DMF (150 mL) was added NaN_3 (1.17 g, 18.12 mmol, 1.2 eq). The mixture was stirred at rt overnight. Then the mixture was poured into water and extracted with EA. The organic solution was dried and concentrated. The residue was purified by flash column chromatography on silica gel column (PE/EA = 10/1, v/v) to give 4-azidomethyl-2,5-difluoro-benzoic acid methyl ester (1.8 g, 52.3%) as a yellow oil.

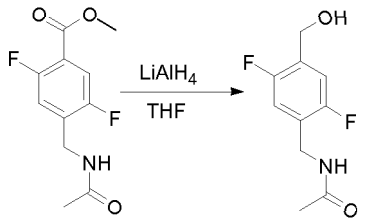


To a solution of compound 4-azidomethyl-2,5-difluoro-benzoic acid methyl ester (1.8 g, 7.9 mmol, 1 eq) in MeOH (80 mL) was added 10% Pd/C (700 mg) and the mixture was stirred under a H_2-filled balloon overnight. Pd/C was removed by filtration and the filtrate was concentrated in vacuo. The residue was directly used without further purification

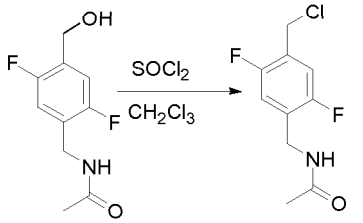


To a solution of compound 4-aminomethyl-2,5-difluoro-benzoic acid methyl ester (1.9 g, 9.4 mmol, 1 eq) and Ac_2O (2.9 g, 28.2 mmol, 3 eq) in CH_2Cl_2 (100 mL) was added TEA (1.9 g, 18.8 mmol, 2 eq) and the mixture was stirred at rt overnight. The mixture was then poured into water and extracted with EA. The organic solution was dried and concentrated. The residue was purified by flash column chromatography (PE/EA =

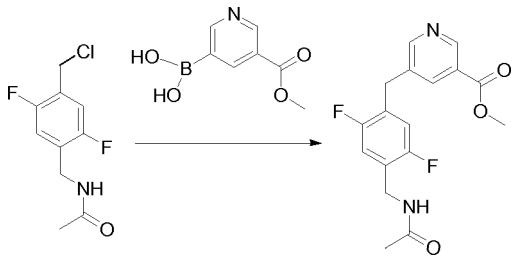
10/1, v/v) to give 4-(acetylamino-methyl)-2,5-difluoro-benzoic acid methyl ester (900 mg, 40%) as a yellow oil.



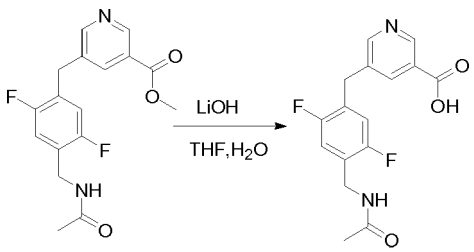
To a solution of compound 4-(acetylamino-methyl)-2,5-difluoro-benzoic acid methyl ester (900 mg, 3.7 mmol, 1 eq) in THF (40 mL) was added $LiAlH_4$ (562 mg, 16.1 mmol, 4 eq). The mixture was stirred at rt for 4 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic solution was dried and concentrated. The residue was purified by flash column chromatography (PE/EA = 10/1, v/v) to give N-(2,5-difluoro-4 –hydroxy methyl-benzyl) –acetamide (600 mg, 75%) as a yellow solid.



To a solution of N-(2,5-difluoro-4-hydroxymethyl-benzyl)-acetamide (350 mg, 0.93 mmol, 1 eq) in $CHCl_3$ (16 mL) was added $SOCl_2$ (0.2 mL) and the mixture was refluxed under heating for 1 h. The solvent was evaporated and the crude product (600mg, quant) was obtained and used directly without further purification.

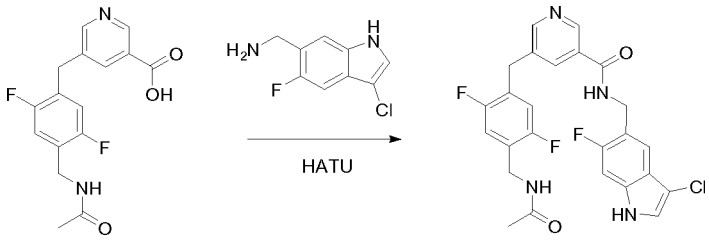


To a solution of N-(4-chloromethyl-2,5-difluoro-benzyl)-acetamide(300 mg, 1.28 mmol, 1.0 eq) and boronic acid (345 mg, 1.92 mmol, 1.5 eq) in dioxane (12 mL) and water (3 mL) was added $Pd(dppf)Cl_2$ (52 mg, 0.06 mmol, 0.05 eq) and Na_2CO_3 (545 mg, 5.12 mmol, 4 eq). The mixture was stirred at 95 °C for 1 h under nitrogen. The solvent was removed in vacuo and the residue was diluted with water and was extracted with EA. The combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (PE/EA = 2/1) to give 5-[4-(acetylamino-methyl)-2,5-difluoro -benzyl]-nicotinic acid methyl ester (100 mg, 23%) as a yellow solid



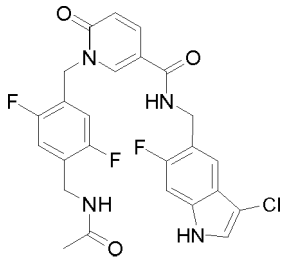
To a solution of 5-[4-(acetylamino-methyl)-2,5-difluoro-benzyl]-nicotinic acid methyl ester (100 mg, 0.29 mmol, 1.0 eq) in THF (4 mL)/ H_2O (0.5 mL) was added $LiOH.H_2O$ (25 mg, 0.07 mmol, 2.0 eq). The mixture

was stirred at 40 °C for 30 min and the solvent was removed in vacuo. The residue was diluted with water and the mixture was acidified to pH 5~6 with 1N HCl solution. The mixture was extracted with DCM and the combined extracts were concentrated in vacuo. The residue (120 mg, yellow solid) was directly used without further purification.

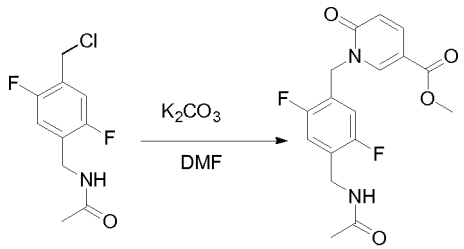


To a solution of 5-[4-(acetylamino-methyl)-2,5-difluoro-benzyl]-nicotinic acid (120 mg, 0.37 mmol, 1.0 eq) and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (96 mg, 0.40 mmol, 1.1 eq) in DCM (4 mL) was added HATU (142 mg, 0.37 mmol, 1.0 eq) and Et_3N (0.26 mL, 1.85 mmol, 5 eq). The mixture was stirred at r.t. for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by prep-HPLC to give 5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1 H-indol-5-yl)methyl)nicotinamide (17 mg, 9.2%) as a white solid. LRMS ($M+H^+$) m/z calculated 501.1, found 501.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.87 (d, 1 H), 8.60 (d, 1 H), 8.12 (s, 1 H), 7.54 (d, 1 H), 7.25 (s, 1 H), 7.16-7.07 (m, 3 H), 4.72 (s, 2 H), 4.37 (s, 2 H), 4.10 (s, 2 H), 1.99 (s, 3 H).

Example 172: Preparation of 1-[4-(Acetylamino-methyl)-2,5-difluoro-benzyl]-6-oxo-1,6 -dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1 H-indol-5-ylmethyl)-amide

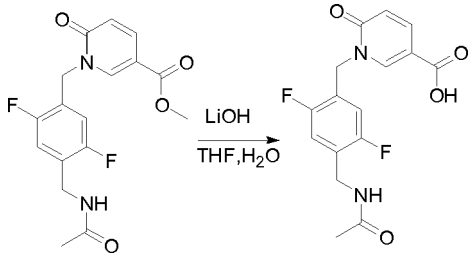


1-[4-(Acetylamino-methyl)-2,5-difluoro-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-amide

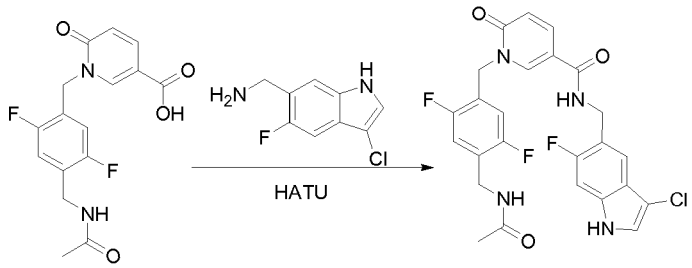


The mixture of compound 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl]-nicotinic acid (140 mg, 0.6 mol, 1 eq), 6-oxo-1,6-dihydro-pyridine-3-carboxylic acid methyl ester and (110 mg, 7.2 mmol, 1.2 eq) and K_2CO_3 (100 mg, 1.2 mmol, 2.0 eq) in DMF (6 mL) was stirred at rt overnight and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (PE/EA = 2/1) to

give 5-[6-(acetylamino-methyl)-pyridin-3-ylmethyl]-N-3-ylmethyl) –nicotinamide (139 mg, 66%) as a yellow solid.

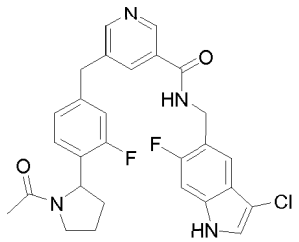


To a solution of 1-[4-(acetylamino-methyl)-2,5-difluoro-benzyl]-6-oxo-1,6-dihydro-pyridine- 3-carboxylic acid methyl ester (18.3 mg, 0.39 mmol, 1.0 eq) in THF (4 mL)/ H_2O (0.5 mL) was added LiOH.H_2O (25 mg, 0.42 mmol, 1.1 eq). The mixture was stirred at 40 °C for 30 min and the solvent was removed in vacuo. The residue was diluted with water and the mixture was acidified to pH 5~6 with 1 N HCl solution. The mixture was extracted with DCM and the combined extracts were concentrated in vacuo. The residue (140 mg, yellow solid) was directly used without further purification.

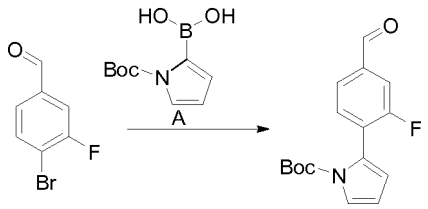


To a solution of 1-[4-(1-[4-(acetylamino-methyl)-2,5-difluoro-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (140 mg, 0.41 mmol, 1.0 eq) and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (107 mg, 0.45 mmol, 1.1 eq) in DCM (4 mL) was added HATU (157 mg, 0.41 mmol, 1.0 eq) and Et_3N (0.22 mL, 1.85 mmol, 1.64 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by prep-HPLC to give acetylamino-methyl)-2,5-difluoro-benzyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1 H-indol-5-ylmethyl)-amide (10.3 mg) as a white solid. LRMS ($M+H^+$) m/z calculated 517.1, found 517.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.87 (d, 1 H), 7.76-7.84 (m, 1 H), 7.41 (d, 1 H), 7.12 (s, 1 H), 7.103-6.95 (m, 3 H), 6.45 (d, 1 H), 5.10 (s, 2 H), 4.56 (s, 2 H), 4.25 (s, 2 H), 1.87 (s, 3 H).

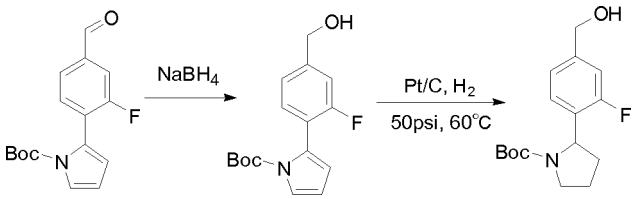
Example 173: Preparation of 5-[4-(1-Acetyl-pyrrolidin-2-yl)-3-fluoro-benzyl]-N-(3-chloro-6 -fluoro-1 H-indol-5-ylmethyl)-nicotinamide



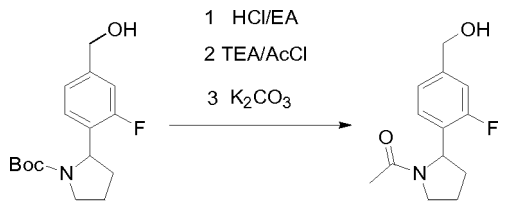
5-[4-(1-Acetyl-pyrrolidin-2-yl)-3-fluoro-benzyl]-*N*-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-nicotinamide



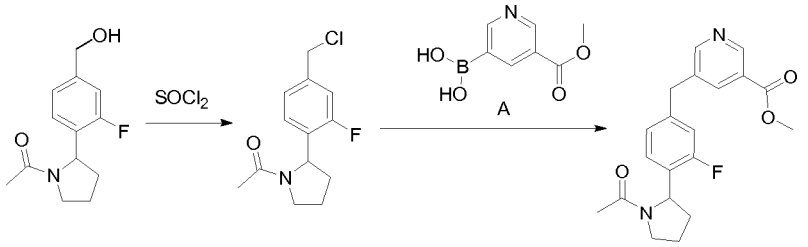
To a solution of 4-bromo-3-fluoro-benzaldehyde (2 g, 9.85 mmol, 1 eq) and boronic acid **A** (2.08 g, 9.85 mmol, 1 eq) in dioxane (100 mL) and water (20 mL) was added Na_2CO_3 (3.13 g, 30 mmol, 3 eq), and $Pd(PPh_3)_4$ (570 mg, 0.49 mmol, 0.05 eq). The mixture was stirred at 100 °C for 3 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (PE/EA = 10/1, v/v) to give 2-(2- fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (1.24 g, 43.6%) as a white solid.



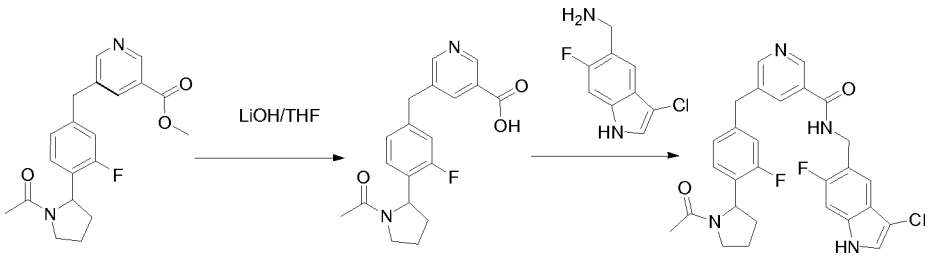
To a solution of 2-(2-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (1.24 g, 4.3 mmol, 1 eq) in MeOH (50 mL) was added $NaBH_4$ (0.32 g, 8.6mmol, 2 eq) portionwise at 0 °C. Then the mixture was stirred at rt for 1 h and diluted with saturated aqueous NH_4Cl solution. The combined mixture was concentrated to remove MeOH and resultant aqueous solution was extracted with DCM, dried and concentrated to give 2-(2-fluoro-4-hydroxymethyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (1.2 g, 99%) as a black solid. To a solution of 2-(2-fluoro-4-hydroxymethyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (1.2 g, 4.3 mmol, 1 eq) in MeOH (40 mL) was added 10% Pd/C (370 mg). The mixture was stirred at 60 °C for 30 h under H_2. Pd/C was removed by filtration and the filtrate was concentrated. The residue was purified by flash chromatography on a silica gel column (EA/ PE = 1/ 5, v/v) to give [6-(tetrahydro-furan-2-yl)-pyridin-3-yl]-methanol (1.2 g, 98.4%) as a colorless oil.



To a solution of [6-(tetrahydro-furan-2-yl)-pyridin-3-yl]-methanol (1.2 g, 4.3 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at r.t. for 0.5 h and the excess reagent was removed by evaporation. To a solution of the residue in DCM (50 mL) was added TEA(1.3 g, 12.9 mmol, 3 eq) and acetyl chloride(1.01 g, 12.9 mmol, 3 eq) at 0 °C. Then the mixture was stirred at r.t. for 3 h, and the excess reagent was removed in vacuo. To a solution of the residue in CH_3OH (50 mL) was added K_2CO_3 (1.12 g, 8.14 mmol, 2 eq), and the mixture was stirred at r.t. for 3 h. The residue was purified by flash chromatography on a silica gel column (EA) to give 1-[2-(2-fluoro-4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone (0.92 g, 56.2%) as a yellow oil.

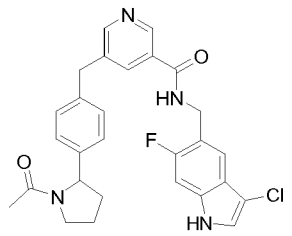


To a solution of the above residue and boronic acid (5 mmol, 1 eq) in dioxane (25 mL) and water (5 mL) was added Na_2CO_3 (1.64 g, 20 mmol, 4 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (158 mg, 0.19 mmol, 0.05 eq). The mixture was stirred at 95 °C for 2 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/ CH_3OH = 10/1, v/v) to give 5-[4-(1-acetyl-pyrrolidin-2-yl)-3-fluoro-benzyl]-nicotinic acid methyl ester (900 mg, 65%) as a black solid.

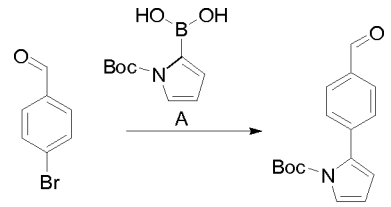


T o a solution of 5-[4-(1-acetyl-pyrrolidin-2-yl)-3-fluoro-benzyl]-nicotinic acid methyl ester (0.1 g, 2.8 mmol, 1 eq) in THF (90 mL) and water (10 mL) was added LiOH (0.015 g, 3.7 mmol, 1.3 eq). The mixture was stirred at 40 °C for 3 h and was acidified to pH 5~6 with 1 N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification. To a solution of 5-[4-(1-acetyl-pyrrolidin-2-yl)-3-fluoro-benzyl]-nicotinic acid (100 mg, 0.28 mmol, 1 eq) and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (66 mg, 0.28 mmol, 1 eq) in DMF (4 mL) was added HATU (117 mg, 0.31 mmol, 1.12 eq), and Et_3N (0.13 g, 1.12 mmol, 4 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/CH_3OH = 10/1, v/v) to give 5-[4-(1-acetyl-pyrrolidin -2-yl)-3-fluoro-benzyl]-N-(3-chloro-6-fluoro-1 H-indol-5-ylmethyl) -nicotinamide (38 mg, 26%) as an off white solid. LRMS ($M+H^+$) m/z calculated 523.1, found 523.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.7 (m, 1 H), 8.5 (m, 1 H), 8.0 (m, 1 H), 7.4 (d, 1 H), 7.1 (d, 1 H), 7.0-6.8 (m, 4H), 5.15 (t, 1 H),4.6 (s, 2 H), 4.6 (d, 2 H), 4.0-3.9 (d, 2 H), 3.56-3.51 (m, 2 H), 2.25-2.05 (m, 1 H), 2.0 (s, 2 H),1.9-1.6 (m,5 H).

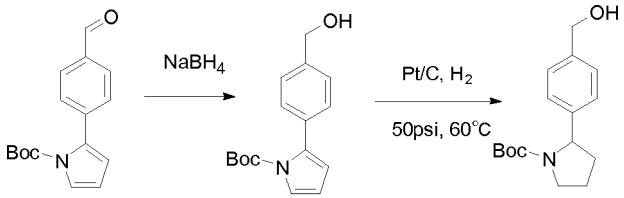
Example 174: Preparation of 5-[4-(1-Acetyl-pyrrolidin-2-yl)-benzyl]-N-(3-chloro-6-fluoro-1 H-indol -5-ylmethyl)-nicotinamide



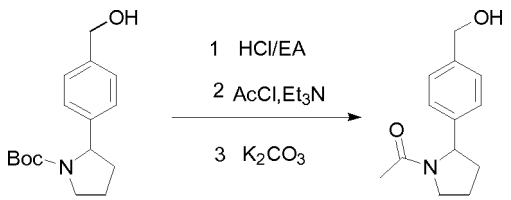
5-[4-(1-Acetyl-pyrrolidin-2-yl)-benzyl]-*N*-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-nicotinamide



To a solution of compound 4-bromo-benzaldehyde (4 g, 21.6 mmol, 1 eq) and 1-*tert*-butoxycarbonylpyrrol-2-yl boronic acid (5.47 g, 25.9 mmol, 1.2 eq) in dioxane (200 mL) and water (40 mL) was added Na_2CO_3 (6.88 g, 65 mmol, 3 eq), and $Pd(PPh_3)_4$ (1.25 g, 1.08 mmol, 0.05 eq). The mixture was stirred at 100 °C for 3 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by falsh chromatography on a silica gel column (PE/EA = 10/1, v/v) to give 2-(4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (4.83 g, 82.4%) as an orange solid.

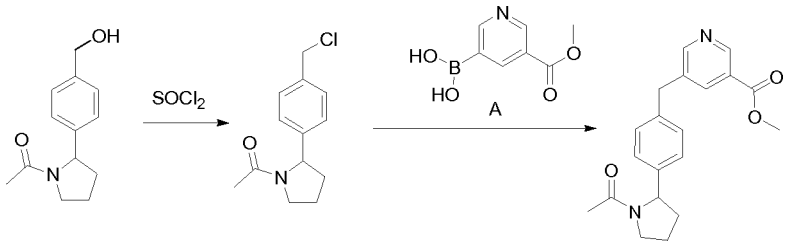


To a solution of 2-(4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (1.24 g, 4.3 mmol, 1 eq) in MeOH (400 mL) was added $NaBH_4$ (1.35 g, 35.6 mmol, 2 eq) portionwise at 0 °C. Then the mixture was stirred at rt for 1 h and diluted with saturated aqueous NH_4Cl solution. The combined mixture was concentrated to remove MeOH and resultant aqueous solution was extracted with DCM, dried and concentrated to give 2-(4-hydroxymethyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (4.5 g, 92%) as a black solid. To a solution of 2-(4-hydroxymethyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (4.5g, 16.5 mmol, 1 eq) in MeOH (160 mL) was added 10% Pd/C (1.35 g). The mixture was stirred at 60 °C for 30 h under H_2. Pd/C was removed by filtration and the filtrate was concentrated. The residue was purified on a silica gel column (EA/PE = 1/5, v/v) to give 2-(4-hydroxymethyl-phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.5 g, 98%) as a colorless oil.

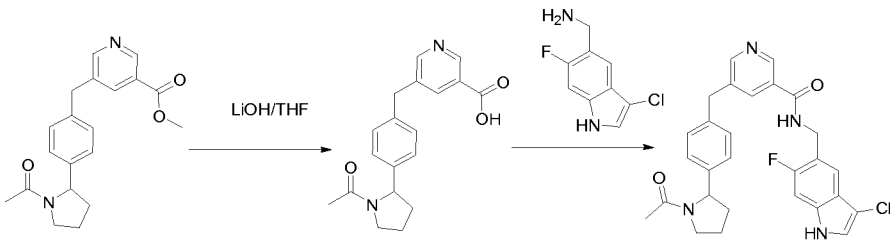


To a solution of 2-(4-hydroxymethyl-phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.5g, 16.5 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 0.5 h and the excess reagent was removed by evaporation. To a solution of the residue in DCM (200 mL) was added TEA(5 g, 49.5 mmol, 3

eq) and acetyl chloride(3.89 g, 49.5 mmol, 3 eq) at 0 °C. Then the mixture was stirred at r.t. for 3 h, and the excess reagent was removed in vacuo. To a solution of the residue in CH_3OH (200 mL) was added K_2CO_3 (4.55 g, 33 mmol, 2 eq), and the mixture was stirred at rt for 3 h. The residue was purified on a silica gel column (EA) to give 1-[2-(4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone (2.1g, 56.2%) as a yellow oil.

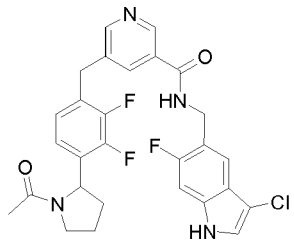


To a solution of 1-[2-(4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone in $CHCl_3$ (100 mL) was add $SOCl_2$ (1.3 g) and the mixture was heated under reflux for 1 h. The excess reagent was removed in vacuo. To a solution of the above residue and boronic acid (11.8 mmol, 1 eq) in dioxane (60 mL) and water (15 mL) was added Na_2CO_3 (3.87 g, 36.5 mmol, 4 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (373 mg, 0.46 mmol, 0.05 eq). The mixture was stirred at 95 °C for 2 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/ CH_3OH = 10/1, v/v) to give 5-[4-(1-acetyl-pyrrolidin-2-yl)-benzyl]-nicotinic acid methyl ester (1.2 g, 39%) as a black solid.

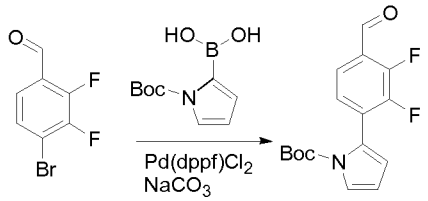


To a solution of 5-[4-(1-Acetyl-pyrrolidin-2-yl)-benzyl]-nicotinic acid methyl ester (0.1 g, 3 mmol, 1 eq) in THF (90 mL) and water (10 mL) was added LiOH (0.016 g, 3.9 mmol, 1.3 eq). The mixture was stirred at 40 °C for 3 h and was acidified to pH 5~6 with 1 N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification. To a solution of 5-[4-(1-acetyl-pyrrolidin-2-yl)-benzyl]-nicotinic acid (100 mg, 0.28 mmol, 1 eq) and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (66 mg, 0.28 mmol, 1 eq) in DMF (4 mL) was added HATU (120 mg, 0.33 mmol, 1.1 eq), and Et_3N (0.13 g, 1.2 mmol, 4 eq). The mixture was stirred at rt for 12 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/CH_3OH = 10/1, v/v) to give 5-[4-(1-acetyl-pyrrolidin-2-yl)-benzyl]-N-(3-chloro-6-fluoro-1 H-indol-5-ylmethyl)-nicotinamide (40 mg, 26.7%) as an white solid. LRMS ($M+H^+$) m/z calculated 505.1, found 505.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.7 (m, 1 H), 8.45 (m, 1 H), 8.0 (m, 1 H), 7.4(d, 1 H), 7.0-6.8 (m, 6 H), 5.15 (t, 1 H),4.6 (s, 2 H), 4.0-3.9 (d, 2 H), 3.56-3.51 (m, 2 H), 2.25-2.05 (m, 1 H), 2.0 (s,1 H), 1.9-1.6 (m,5 H).

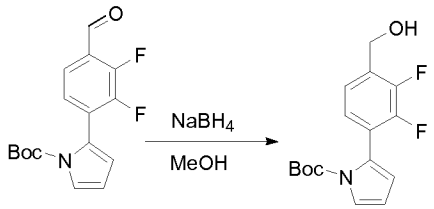
Example 175: Preparation of 5-(4-(1-acetylpyrrolidin-2-yl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro- 1 H-indol-5-yl)methyl)nicotinamide



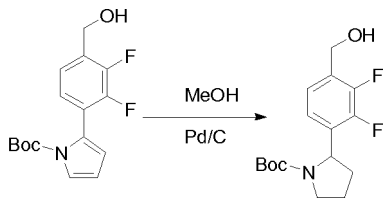
5-[4-(1-Acetyl-pyrrolidin-2-yl)-2,3-difluoro-benzyl]-*N*-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-nicotinamide



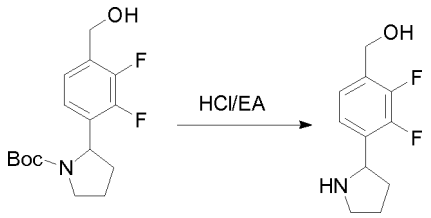
To a solution of 4-bromo-2,3-difluoro-benzaldehyde (4.3 g, 19.5 mmol, 1.0 eq) in dioxane (50 mL) was added boronic acid **B** (4.11 g, 19.5 mmol, 1.0 eq), $Pd(dppf)Cl_2CH_2Cl_2$ (1.7 g, 1.95 mmol, 0.1 eq), Na_2CO_3 (6.2 g, 58.5 mmol, 3.0 eq) and H_2O (10 mL) . The mixture was stirred at 95 °C for 2 h and allowed cool to rt. The reaction mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to flash chromatography (PE/EA = 5/1-2/1, v/v) to afford 2-(2,3-difluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester as a yellow oil (2.3 g, 38.3%).



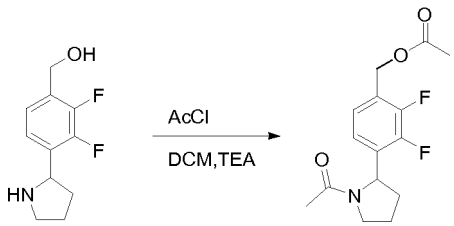
The mixture of 2-(2,3-difluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (2.3 g, 7.5 mmol, 1.0 eq) and $NaBH_4$ (0.57 g, 15.0 mmol, 2.0 eq) in MeOH (50 mL) was stirred at rt for 2 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product 2-(2,3-difluoro-4-hydroxymethyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester as a yellow oil (2.25 g, 98%).



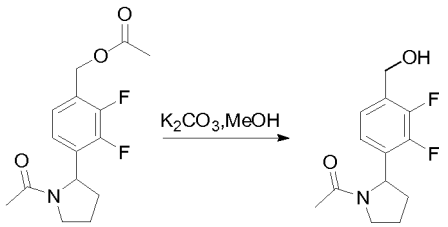
The mixture of 2-(2,3-difluoro-4-hydroxymethyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (2.25 g, 7.28 mmol, 1.0 eq) and Pd/C (0.4 g, 20%) in MeOH (50 mL) was stirred at 60 °C for 30 h under the atmosphere of H_2 (60 psi). The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product 2-(2,3-difluoro-4-hydroxymethyl-phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester as a white solid (2.0 g, 89%).



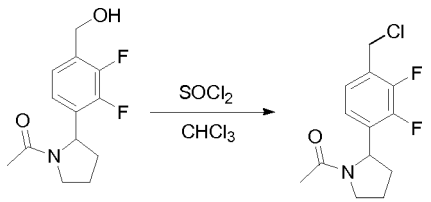
The mixture of 2-(2,3-difluoro-4-hydroxymethyl-phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.0 g, 6.4 mmol, 1.0 eq) in MeOH (50 mL) was added HCl. The mixture was stirred at rt for 1 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product (2,3-difluoro-4-pyrrolidin-2-yl-phenyl)-methanol as a white solid (crude 1.9 g, quant).



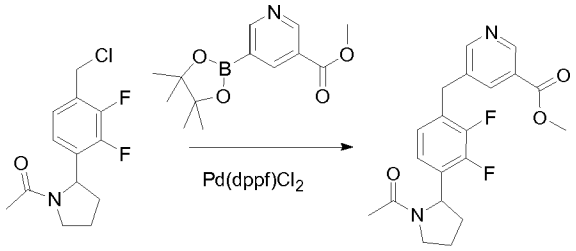
The mixture of (2,3-difluoro-4-pyrrolidin-2-yl-phenyl)-methanol (1.9 g, 6.4 mmol, 1.0 eq), AcCl (2.02 g, 25.6 mmol, 4.0 eq) and TEA (2.59 g, 25.6 mmol, 4.0 eq) in DCM (50 mL). The mixture was stirred at rt for 1 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product acetic acid 4-(1-acetyl-pyrrolidin-2-yl)-2,3-difluoro-benzyl ester as a white solid (crude 2.1 g, quant).



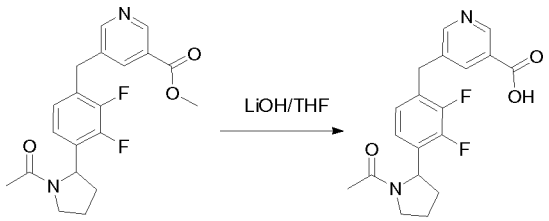
To a solution of acetic acid 4-(1-acetyl-pyrrolidin-2-yl)-2,3-difluoro-benzyl ester (2.1 g, 6.4 mmol, 1.0 eq) in MeOH (30 mL) was added K_2CO_3 (1.77 g, 12.8 mmol, 2.0 eq). The mixture was stirred at rt for 2 h. The reaction mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to flash chromatography (PE/EA = 3/1-1/1, v/v) to afford 1-[2-(2,3-difluoro-4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone as a yellow oil (1.37 g, 84%).



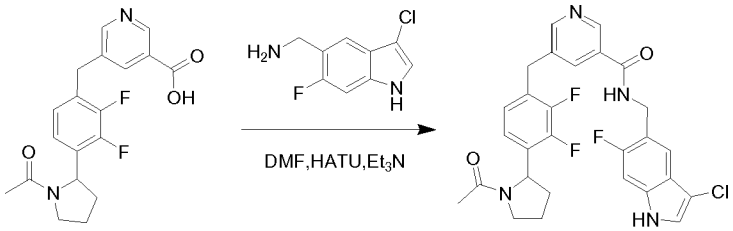
To a solution of 1-[2-(2,3-difluoro-4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone (1.37 g, 5.37 mmol, 1.0 eq) in$CHCl_3$ (30 mL) was added $SOCl_2$ (0.96 g, 8.06 mmol, 1.2 eq). The mixture was stirred at 80 °C for 2 h. The reaction mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to flash chromatography (PE/EA = 5/1-3/1, v/v) to afford 1-[2-(4-chloromethyl-2,3-difluoro-phenyl)-pyrrolidin-1-yl]-ethanone as a white solid (1.36 g, 92.5%).



To a solution of 1-[2-(4-chloromethyl-2,3-difluoro-phenyl)-pyrrolidin-1-yl]-ethanone (0.36 g, 1.31 mmol, 1.0 eq) in dioxane (10 mL) was added 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinic acid methyl ester (0.34 g, 1.31 mmol, 1.0 eq), $Pd(dppf)Cl_2CH_2Cl_2$ (114 mg, 0.13 mmol, 0.1 eq), Na_2CO_3 (417 mg, 3.93 mmol, 3.0 eq) and H_2O (2 mL) . The mixture was stirred at 95 °C for 2 h and allowed cool to r.t. The reaction mixture was extracted with EtOAc (100 mL ×3). The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to flash chromatography (PE/EA = 5/1 - 1/1) to afford 5-[4-(1-acetyl-pyrrolidin-2-yl)-2,3-difluoro-benzyl]-nicotinic acid methyl ester as a yellow oil (0.4 g, 81.6%).

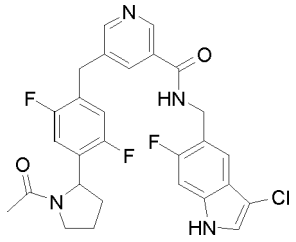


To a solution of 5-[4-(1-acetyl-pyrrolidin-2-yl)-2,3-difluoro-benzyl]-nicotinic acid methyl ester (400 mg, 1.07 mmol, 1.0 eq) in THF (5 mL) and H_2O (1 mL) was added the $LiOH•H_2O$ (90 mg, 2.14 mmol, 2.0 eq). The reaction mixture was stirred for 1 h at rt. Water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give 5-[4-(1-acetyl-pyrrolidin-2-yl)-2,3-difluoro-benzyl]-nicotinic acid as a yellow oil (360 mg, 93.3%), which was used directly without further purification.

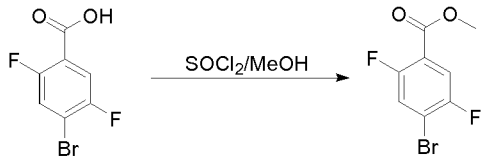


To a solution of 5-[4-(1-acetyl-pyrrolidin-2-yl)-2,3-difluoro-benzyl]-nicotinic acid (100 mg, 0.317 mmol, 1.0 eq) in DMF (5 mL) was added C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (70 mg, 0.317 mmol, 1.0 eq) followed by HATU (144 mg, 0.38 mmol, 1.2 eq) and TEA (160 mg, 1.58 mmol, 5.0 eq). The reaction mixture was stirred overnight at r.t. LCMS showed the SM was consumed. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give 5-[4-(1-acetyl-pyrrolidin-2-yl)-2,3-difluoro-benzyl]-N-(3-chloro-6-fluoro-1 H-indol-5-ylmethyl)-nicotinamide (60 mg, 35.3%) as a white solid. LRMS ($M+H^+$) m/z calculated 541.1, found 541.1.^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.69-1.94 (m, 4 H), 2.00 (s, 2 H), 2.18-2.33 (m, 1 H), 3.40-3.75 (m, 2 H), 4.10 (d,2 H), 4.59 (d, 2 H), 5.10-5.24 (m, 1 H), 6.86-6.92 (m, 1 H), 7.04-7.17 (m, 1 H), 7.22 (d, 1 H), 7.45 (d, 1 H), 7.50 (d,1 H), 8.08 (s, 1 H). 8.64 (s, 1 H), 8.92 (s,1 H), 9.18 (t, 1 H).11.39 (s,1 H)

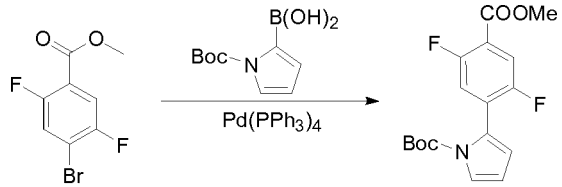
Example 176: Preparation of 5-(4-(1-acetylpyrrolidin-2-yl)-2,5-difluorobenzyl)-N-((3-chloro-6-fluoro- 1 H-indol-5-yl)methyl)nicotinamide



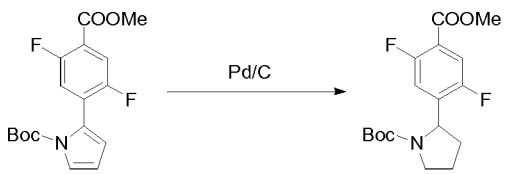
5-(4-(1-acetylpyrrolidin-2-yl)-2,5-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide



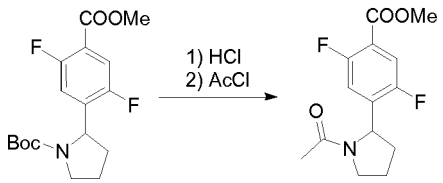
To a solution of 4-bromo-2,5-difluoro-benzoic acid (5.0 g, 21.18 mmol, 1 eq) in dry MeOH (70 mL) was added $SOCl_2$ (3.1 mL, 42.36 mmol, 2 eq). The mixture was stirred at 70 °C for 3 h and the excess reagent was removed in vacuo. The residue was diluted with EA and washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried and concentrated to give 4-bromo-2,5-difluoro-benzoic acid methyl ester (4.7 g, 89%) as a gray solid.



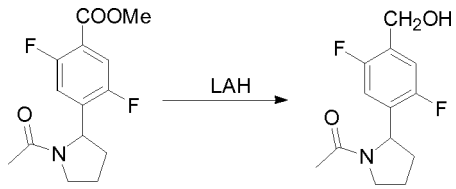
To a solution of 4-bromo-2,5-difluoro-benzoic acid methyl ester (3.23 g, 12.93 mmol, 1 eq) and N-boc-2-pyrroleboronic acid (3.0 g, 14.22 mmol, 1.1 eq) in dioxane (60 mL) and water (15 mL) was added $Pd(PPh_3)_4$ (747 mg, 0.647 mmol, 0.05 eq) and Na_2CO_3 (4.12 g, 38.79 mmol, 3 eq). The mixture was stirred at 95 °C for 4 h under nitrogen. The mixture was allowed to cool to rt. The solvent was removed in vacuo and the residue was diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (EA/PE = 1/40, v/v) to give 2-(2,5-difluoro-4-methoxycarbonyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (3.0 g, 69%) as a colorless oil.



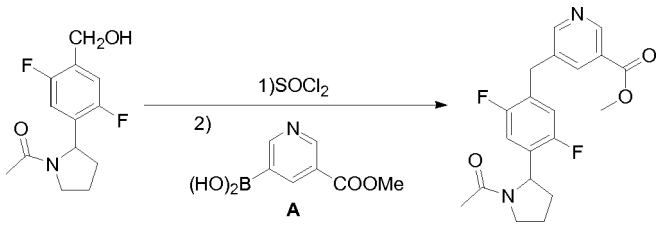
To a solution of 2-(2,5-difluoro-4-methoxycarbonyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (3.0 g, 9.34 mmol, 1 eq) in MeOH (50 mL) was added 10% Pd/C (900 mg). The mixture was stirred at 50 psi and 40 °C under H_2 for 24 h. Pd/C was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column (EA/PE = 1/20, v/v) to give 2-(2,5-difluoro-4-methoxycarbonyl-phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.95 g, 64%) as a colorless oil.



To a solution of 2-(2,5-difluoro-4-methoxycarbonyl-phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.95 g, 6 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 1 h and was concentrated in vacuo. The residue was re-dissolved in dry DCM (60 mL). To the solution was added AcCl (1.3 mL, 18 mmol, 3 eq) and Et_3N (3.3 mL, 24 mmol, 4 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with water. The organic layer was separated and washed with 1N HCl solution and brine. The mixture was dried and concentrated in vacuo to give 4-(1-acetyl-pyrrolidin-2-yl)-2,5-difluoro-benzoic acid methyl ester (1.6 g, 94% for 2 steps) as a brown oil.

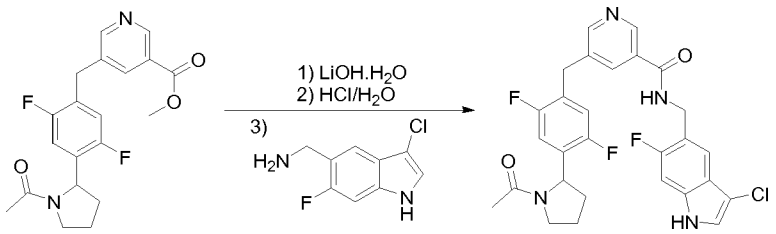


To a solution of 4-(1-acetyl-pyrrolidin-2-yl)-2,5-difluoro-benzoic acid methyl ester (1.60 g, 5.65 mmol, 1 eq) in dry THF (50 mL) was added LAH (650 mg, 17 mmol, 3 eq). The mixture was stirred at 0 °C for 1 h and was quenched by the addition of EA. The mixture was concentrated in vacuo and the residue was diluted with water. The mixture was extracted with EA and the combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (EA) to give 1-[2-(2,5-difluoro-4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone (250 mg, 17%) as a yellow oil.



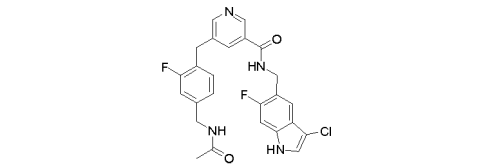
To a solution of 1-[2-(2,5-difluoro-4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone (180 mg, 0.70 mmol, 1 eq) in $CHCl_3$ (5 mL) was added $SOCl_2$ (0.05 mL, 0.85 mmol, 1.2 eq). The mixture was stirred at 60 °C for 1 h and the excess reagent was removed by evaporation.

To a solution of the above residue and boronic acid **A** (0.85 mmol, 1.2 eq) in dioxane (4.2 mL) and water (1.0 mL) was added Na_2CO_3 (300 mg, 2.82 mmol, 4 eq) and $Pd(dppf)Cl_2$ (29 mg, 0.035 mmol, 0.05 eq). The mixture was stirred at 95 °C for 1 h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (EA/PE = 2/1, v/v) to give 5-[4-(1-acetyl-pyrrolidin-2-yl)-2,5-difluoro-benzyl]-nicotinic acid methyl ester (90 mg, 34% yields for 2 steps) as a yellow solid.

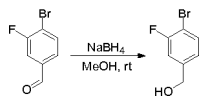


To a solution of 5-[4-(1-acetyl-pyrrolidin-2-yl)-2,5-difluoro-benzyl]-nicotinic acid methyl ester (90 mg, 0.24 mmol, 1.0 eq) in THF (5 mL)/ H_2O (1 mL) was added LiOH.H_2O (12 mg, 0.29 mmol, 1.2 eq). The mixture was stirred at 40 °C for 1 h and was acidified to pH 5 with 1 N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification. To a solution of the above crude product and C-(3-chloro-6-fluoro-1 H-indol-5-yl)-methylamine (57 mg, 0.24 mmol, 1 eq) in DCM (4 mL) was added HATU (92 mg, 0.29 mmol, 1.2 eq) and Et_3N (0.13 mL, 0.96 mmol, 4 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/MeOH = 20/1, v/v) to give 5-(4-(1-acetylpyrrolidin-2-yl)-2,5-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide (90 mg, 69% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 541.1, found 541.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.76-8.74 (m, 1 H), 8.50-8.47 (m, 1 H), 8.00 (s, 1 H), 7.41 (d, 1 H), 7.12 (s, 1 H), 7.06-6.93 (m, 2 H), 6.79-6.72 (m, 1 H), 5.15-5.08 (m, 1 H), 4.59 (s, 2 H), 3.99 (s, 1 H), 3.95 (s, 1.3 H), 3.74-3.49 (m, 2 H), 2.32-2.16 (m, 1 H), 2.02 (s, 2 H), 1.90-1.71 (m, 3 H), 1.72 (s, 1 H).

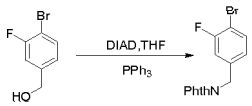
Example 177: Preparation of 5-[4-(acetylamino-methyl)-2-fluoro-benzyl]-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide



5-[4-(Acetylamino-methyl)-2-fluoro-benzyl]-*N*-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-nicotinamide

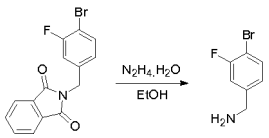


To a solution of 4-bromo-3-fluoro-benzaldehyde (10.1 g, 49.8 mmol, 1.0 eq) in MeOH (100 mL) was added $NaBH_4$ (3.8 g, 99.6 mmol, 2.0 eq). The mixture was stirred at rt for 2 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product (4-bromo-3-fluoro-phenyl)-methanol (10.3 g, 100%).

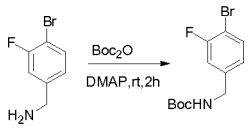


The mixture of (4-bromo-3-fluoro-phenyl)-methanol (10.3 g, 50.0 mmol, 1.0 eq), PPh_3 (15.7 g, 60.0 mmol, 1.2 eq) and DIAD (12.1 g, 60.0 mmol, 1.2 eq) in THF (100 mL) was stirred at rt for 12 h. The reaction was quenched with H_2O. The reaction mixture was extracted with ethyl acetate, and the organic was washed with brine, dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel

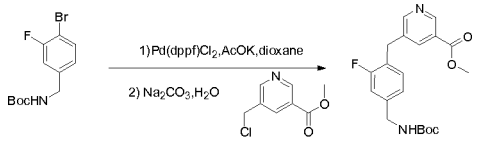
chromatography (PE/EA = 10/1-5/1, v/v) to afford 2-(4-bromo-3-fluoro-benzyl)-isoindole-1,3-dione (16.4 g, 98%) as a white solid.



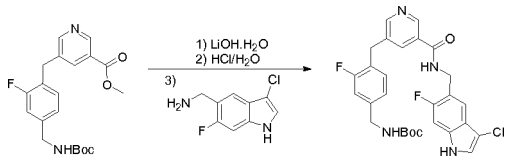
To a solution of 2-(4-bromo-3-fluoro-benzyl)-isoindole-1,3-dione (5.0 g, 15.0 mmol, 1.0 eq) in EtOH (100 mL) was added N_2H_4. H_2O (3.75 g, 75 mmol, 5.0 eq). The reaction mixture was stirred at rt for 1 h. The solvent was removed in vacuo, and the residue was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and evaporated to give the crude product which was subject to silica gel chromatography (PE/EA = 3/1~1/1, v/v) to afford 4-bromo-3-fluoro-benzylamine (1.5 g, 46%) as a yellow oil.



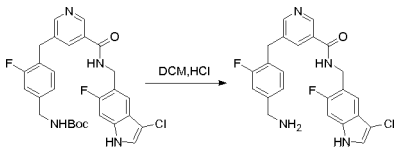
To a solution of 4-bromo-3-fluoro-benzylamine (1.5 g, 7.35 mmol, 1.0 eq) in THF (50 mL) was added Boc_2O (3.2 g, 14.7 mmol, 2.0 eq) and DMAP (96 mg, 0.74 mmol, 0.1 eq). The mixture was stirred at rt for 2 h. The reaction mixture was extracted with ethyl acetate, washed with brine and water. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product which was subject to silica gel chromatography (PE/EA = 20/1~10/1, v/v) to afford (4-bromo-3-fluoro-benzyl)-carbamic acid *tert*-butyl ester (800 mg, 36%) as a white solid.



5-[4-(*tert*-Butoxycarbonylamino-methyl)-2-fluoro-benzyl]-nicotinic acid methyl ester (1.0 g, 41%) was prepared as described for 5-(6-hydroxy methyl-pyridin-3-ylmethyl)-nicotinic acid methyl ester.

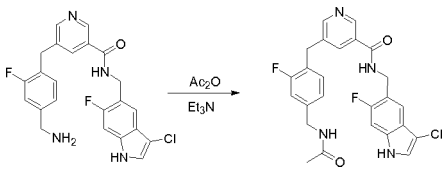


(4-{5-[(3-Chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-3-fluoro-benzyl)-carbamic acid *tert*-butyl ester (500 mg, 100%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide.



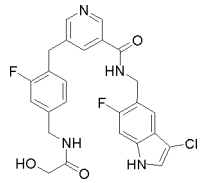
To a solution of (4-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-3-fluoro-benzyl)-carbamic acid *tert*-butyl ester (500 mg, 0.93 mmol, 1.0 eq) in DCM (20 mL) was added HCl (80 mg, 2.3 mmol, 2.0 eq). The reaction mixture was stirred at rt for 1 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to give 5-(4-aminomethyl-2-

fluoro-benzyl)-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide was used without purification (440 mg, 98%) as a white solid.

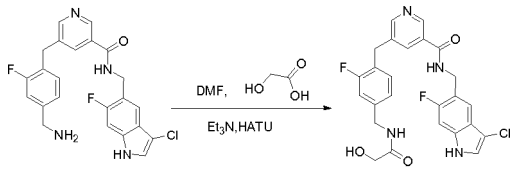


To a solution of 5-(4-aminomethyl-2-fluoro-benzyl)-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide (100 mg, 0.23 mmol, 1.0 eq) in DCM (10 mL) was added Et_3N (47 mg, 0.46 mmol, 2.0 eq) and Ac_2O (100 mg, 0.46 mmol, 2.0 eq). The reaction mixture was stirred at rt for 1 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give 5-[4-(acetylamino-methyl)-2-fluoro-benzyl]-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide (30 mg, 27%) as a white solid. LRMS ($M+H^+$) m/z calculated 483.1, found 483.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.38 (s, 1 H), 9.17 (d, 1 H), 8.90 (d, 1 H), 8.61 (d, 1 H), 8.32 (s, 1 H), 8.02 (s, 1 H), 7.50 (d, 1 H), 7.45 (d, 1 H), 7.31 (t, 1 H), 7.21 (d, 1 H), 7.04 (d, 2 H), 4.58 (s, 2 H), 4.21 (d, 2 H), 4.04 (s, 2 H), 1.85 (s, 3 H).

Example 178: Preparation of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-{2-fluoro-4-[(2-hydroxy-acetylamino)-methyl]-benzyl}-nicotinamide

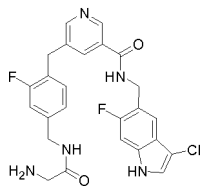


N-(3-Chloro-6-fluoro-1*H*-indol-5-ylmethyl)-5-{2-fluoro-4-[(2-hydroxy-acetylamino)-methyl]-benzyl}-nicotinamide



To a solution of 5-(4-aminomethyl-2-fluoro-benzyl)-N-(3-chloro-6-fluoro-1H- indol-5-ylmethyl)-nicotinamide (100 mg, 0.23 mmol, 1.0 eq) in DMF (10 mL) was added Et_3N (47 mg, 0.46 mmol, 2.0 eq), hydroxy-acetic acid (34 mg, 0.46 mmol, 2.0 eq) and HATU (105 mg, 0.28 mmol, 1.2 eq). The reaction mixture was stirred at rt for 1 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give 5-{4-[(2-amino-acetylamino)-methyl]-2-fluoro-benzyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide (30 mg, 27%) as a white solid. LRMS ($M+H^+$) m/z calculated 498.1, found 498.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.38 (s, 1 H), 9.16 (s, 1 H), 8.90 (d, 1 H), 8.61 (d, 1 H), 8.31(t, 1 H), 8.01 (s, 1 H), 7.50 (s, 1 H), 7.45 (d, 1 H), 7.29 (t, 1 H), 7.22 (d, 2 H), 7.06 (d, 2 H), 5.48 (t, 1 H), 4.58 (s, 2 H), 4.26 (d, 2 H), 4.03 (s, 2 H), 3.84 (d, 2 H).

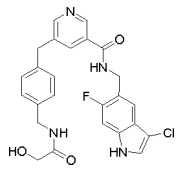
Example 179: Preparation of 5-{4-[(2-amino-acetylamino)-methyl]-2-fluoro-benzyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide



5-{4-[(2-Amino-acetylamino)-methyl]-2-fluoro-benzyl}-*N*-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-nicotinamide

5-{4-[(2-Amino-acetylamino)-methyl]-2-fluoro-benzyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide (18 mg, 17%) was prepared as described for 5-{4-[(2-amino-acetylamino)-methyl]-2-fluoro-benzyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide. LRMS (M+H$^+$) m/z calculated 497.1, found 497.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.17 (t, 1 H), 8.90 (d, 1 H), 8.61 (d, 1 H), 8.32 (s, 1 H), 8.02 (s, 1 H), 7.44-7.50 (m, 2 H), 7.06 (d, 2 H), 4.58 (s, 2 H) ,4.26 (d, 2 H), 4.03 (s, 2 H), 3.12 (s, 2 H), 4.03 (s, 2 H).

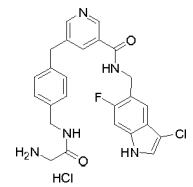
Example 180: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-hydroxyacetamido)methyl)benzyl)nicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-5-(4-((2-hydroxyacetamido)methyl)benzyl)nicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-hydroxyacetamido)methyl)benzyl)nicotinamide (50 mg, 87%) was prepared as described for 5-{4-[(2-amino-acetylamino)-methyl]-2-fluoro-benzyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide as a white solid. LRMS (M+H+) m/z calculated 481.1, found 481.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.16 (t, 1 H), 8.90 (s, 1 H), 8.64 (s, 1 H), 8.21 (t,1 H), 8.06 (s, 1 H), 7.51 (d, 1 H), 7.47 (d, 1 H), 7.24 (s, 1 H), 7.21 (s, 4 H), 5.45 (t, 1 H), 4.59 (d, 2 H), 4.26 (d, 2 H), 4.01 (s, 2 H), 3.84 (d, 2 H).

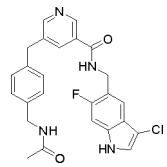
Example 181: Preparation of 5-(4-((2-aminoacetamido)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide



5-(4-((2-aminoacetamido)methyl)benzyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)nicotinamide hydrochloride

5-(4-((2-Aminoacetamido)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide hydrochloride (40 mg, 80%) was prepared as described for 5-(4-aminomethyl-benzyl)-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide as a light yellow solid. LRMS (M+H$^+$) m/z calculated 480.1, found 480.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.48 (s, 1 H), 9.40 (t, 1 H), 9.04 (s, 1 H), 8.86 (t, 1 H), 8.79 (d, 1 H), 8.37 (s, 1 H), 8.11 (s, 3 H), 7.51 (d, 1 H), 7.48 (d, 1 H), 7.25 (s, 5 H) , 4.60 (d, 2 H), 4.29 (d, 4 H), 4.10 (s, 2 H), 3.57 (q, 2 H).

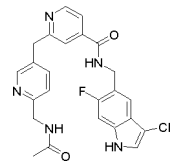
Example 182: Preparation of 5-(4-(acetamidomethyl)-3-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl) nicotinamide



5-(4-(acetamidomethyl)-3-fluorobenzyl)-*N*-((3-chloro-6-fluoro-1*H*-indol -5-yl)methyl)nicotinamide

5-(4-(Acetamidomethyl)-3-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide (50 mg, 44%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 483, found 483. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (br, 1 H), 9.15 (t, 1 H), 8.90 (d, 1 H), 8.65 (d, 1 H), 8.25 (t, 1 H), 8.08 (t, 1 H), 7.50 (d, 1 H), 7.46 (d, 1 H), 7.21-7.26 (m, 2 H), 7.07-7.14 (m, 2 H), 4.59 (d, 2 H), 4.22 (d, 2 H), 4.03 (s, 2 H), 1.83 (s, 3 H).

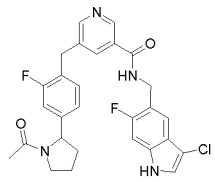
Example 183: Preparation of 2-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



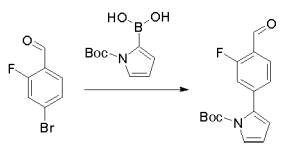
2-((6-(acetamidomethyl)pyridin-3-yl)methyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)isonicotinamide

2-((6-(Acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide 2,2,2-trifluoroacetate (25 mg, 29% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)- pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 467.1, found 467.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.69 (d, 1 H) 8.62 (d, 1 H), 8.38 (d, 1 H), 7.83 (s, 1 H), 7.81 (d, 1 H), 7.71 (dd, 1 H), 7.50 (d, 1 H), 7.22 (s, 1 H), 7.11 (d, 1 H), 4.69 (s, 2 H),4.62 (s, 2 H), 4.41 (s, 2 H), 2.03 (s, 3 H).

Example 184: Preparation of methyl 5-(4-(1-acetylpyrrolidin-2-yl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide

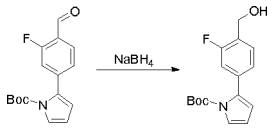


5-(4-(1-acetylpyrrolidin-2-yl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide

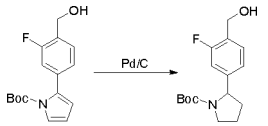


To a solution of 4-bromo-2-fluoro-benzaldehyde (4 g, 19.7 mmol, 1 eq) and N-Boc-2-pyrroleboronic acid (5.4 g, 25.61 mmol, 1.3 eq) in dioxane (160 mL) and water (40 mL) was added $Pd(PPh_3)_4$ (1.48 g, 1.28 mmol, 0.05 eq) and Na_2CO_3 (6.26 g, 59.10 mmol, 3 eq). The mixture was stirred at 95 °C for 2 h under nitrogen. The mixture was allowed to cool to rt. The solvent was removed in vacuo and the residue was diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column

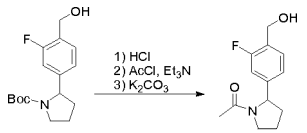
(EA/PE = 1/5, v/v) to give 2-(3-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (4.4 g, 77%) as a yellow solid.



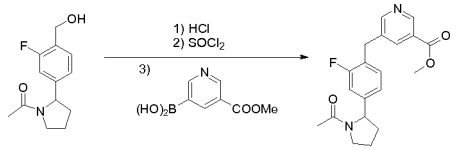
To a solution of 2-(3-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (4.5 g, 15.60 mmol, 1 eq) in MeOH (150 mL) was added $NaBH_4$ (1.18 g, 31.20 mmol, 2 eq) portionwise at 0 °C. Then the mixture was stirred at rt for 1 h and diluted with saturated aqueous NH_4Cl solution. The combined mixture was concentrated to remove MeOH and resultant aqueous solution was extracted with DCM, dried and concentrated to give 2-(3-fluoro-4-hydroxymethyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (4 g, quant).



To a solution of 2-(3-fluoro-4-hydroxymethyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (4 g, 13.7 mmol, 1 eq) in MeOH (100 mL) was added 10% Pd/C (3 g). The mixture was stirred at 40 °C under H_2 (50 psi) for 30 h. Pd/C was removed by filtration and the filtrate was concentrated to give 2-(3-fluoro-4-hydroxymethyl-phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.5 g, 86%) as a yellow oil.

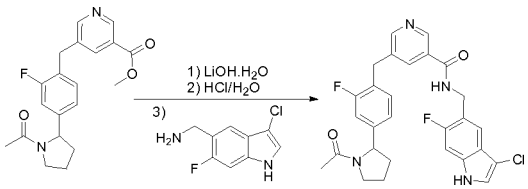


To a solution of 2-(3-fluoro-4-hydroxymethyl-phenyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4.7 g, 15.93 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 1 h and was concentrated in vacuo. The residue was redissolved in dry DCM (150 mL) and to this solution was added AcCl (7.2 g, 47.79 mmol, 3 eq) and Et_3N (13 mL, 63.72 mmol, 4 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with water. The organic layer was separated and washed with 1 N HCl solution and brine. The mixture was dried and concentrated in vacuo. To the above crude product in MeOH (100 mL) was added K_2CO_3 (4.39 g, 31.86 mmol, 2 eq). The mixture was stirred at rt for 3 h and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (EA/PE = 1/1, v/v) to give 1-[2-(3-fluoro-4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone (3 g, 79% yields for 3 steps) as a yellow oil.



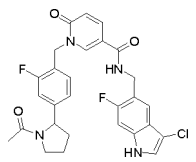
To a solution of 1-[2-(3-fluoro-4-hydroxymethyl-phenyl)-pyrrolidin-1-yl]-ethanone (1 g, 4.21 mmol, 1 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 0.5 h and the excess reagent was removed by evaporation. The residue was treated with $SOCl_2$ (5 mL) and the mixture was heated under reflux for 1h. The excess reagent was removed in vacuo. To the above residue and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinic acid methyl ester (6.31 mmol, 1.5 eq) in dioxane (40 mL) and water (10 mL) was added Na_2CO_3 (1.7 g, 16.84 mmol, 4 eq) and $Pd(dppf)Cl_2$ (0.17 g, 0.21 mmol, 0.05 eq). The mixture was stirred at 90 °C for 2

h under nitrogen. The mixture was allowed to cool to rt and diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/MeOH = 20/1, v/v) to give 5-[4-(1-acetyl-pyrrolidin-2-yl)-2-fluoro-benzyl]-nicotinic acid methyl ester (284 mg, 19% yields for 3 steps) as a brown oil.



5-(4-(1-Acetylpyrrolidin-2-yl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide (106 mg, 25% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 523.1, found 523.1. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.81 (s, 2 H), 8.58 (s, 0.54 H), 8.47 (s, 0.46 H), 7.80 (s, 0.54 H), 7.93 (s, 0.46 H), 7.59-7.56 (m, 1 H), 7.12-7.08 (m, 1.5 H), 7.00-6.92 (m,2 H), 6.87-6.76 (m, 2.5 H), 5.12 (dd, 0.46 H), 4.85 (dd, 0.54 H), 4.76-4.72 (m, 2 H), 4.00 (s, 1 H), 3.90 (s, 1 H), 3.72-3.57 (m, 2 H), 2.45-2.25 (m, 2 H), 2.12 (s, 1 H), 1.97-1.80 (m, 4 H), 1.81 (s, 2 H).

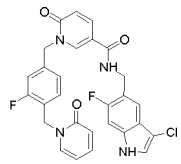
Example 185: Preparation of 1-(4-(1-acetylpyrrolidin-2-yl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



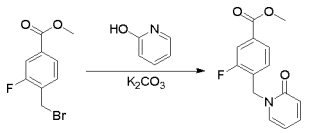
1-(4-(1-acetylpyrrolidin-2-yl)-2-fluorobenzyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide

1-(4-(1-Acetylpyrrolidin-2-yl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (70 mg, 49% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin- 2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS (M+H+) m/z calculated 539.1, found 539.1. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.12 (s, 0.6 H), 8.97 (s, 0.4 H), 8.21 (s, 0.4 H), 8.18 (s, 0.6 H), 7.73-7.66 (m, 1 H), 7.52-7.45 (m, 1.6 H), 7.06-6.67 (m, 5 H), 6.42 (d, 0.4 H), 6.36 (d, 0.6 H), 5.08 (s, 1 H), 4.97-4.83 (m, 2 H), 4.66-4.61 (m, 2 H), 3.67-3.50 (m, 2 H), 2.36-2.06 (m, 2 H), 2.09 (s, 1.2 H), 1.90-1.72 (m, 4 H), 1.77 (s, 1.8 H).

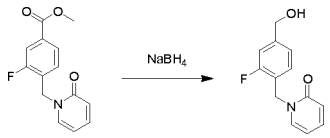
Example 186: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



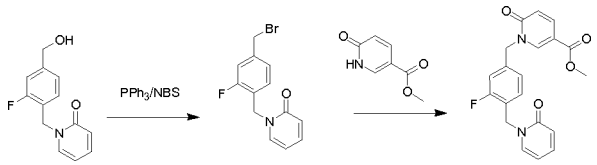
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide



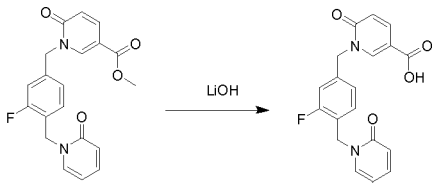
To a mixture of pyridin-2-ol (311 mg, 3.27 mmol, 1.05 eq) in DMF (5 mL) was added K_2CO_3 (862 mg, 6.24 mmol, 2.0 eq) followed by methyl 4-(bromomethyl)-3-fluorobenzoate (770 mg, 3.12 mmol, 1.0 eq). The resultant mixture was stirred for 2 h, and then water (80 mL) was added. The mixture was extracted with EA and the organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on a silica gel (PE~PE/EA = 2/1, v/v) to give methyl 3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate (650 mg, 80%) as a white solid. LRMS ($M+H^+$) m/z calculated 262, found 262.



The mixture of methyl 3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate (650 mg, 2.49 mmol, 1.0 eq) in MeOH (30 mL) was added $NaBH_4$ (1.9 g, 49.80 mmol, 20.0 eq). The resultant mixture was kept stirring at rt for overnight. The reaction mixture was concentrated. The residue was purified by chromatography on a silica gel column (DCM~DCM/MeOH = 10/1, v/v) to give 1-(2-fluoro-4-(hydroxyl methyl)benzyl)pyridin-2(1H)-one (150 mg, 25%) as a colorless oil. LRMS ($M+H^+$) m/z calculated 234, found 234.

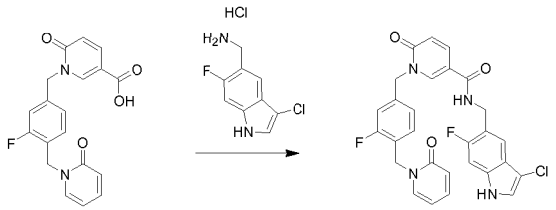


To a mixture of 1-(2-fluoro-4-(hydroxyl methyl)benzyl)pyridin-2(1H)-one (150 mg, 0.64 mmol, 1.0 eq) in DCM (10 mL) was added PPh_3 (253 mg, 0.96 mmol, 1.5 eq) followed by NBS (125 mg, 0.70 mmol, 1.1 eq). The reaction mixture kept stirring for 2 h and the mixture was concentrated. The residue was added to the mixture of methyl 6-oxo-1, 6-dihydropyridine-3- carboxylate (98 mg, 0.64 mmol, 1.0 eq) and K_2CO_3 (176 mg,1.28 mmol, 2.0 eq) in DMF (10mL). The resultant mixture was stirred for 2 h. Water (20 mL) was added and the mixture was extracted with EA. The organic phase was dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on a silica gel column (PE~PE/EA = 10/1 to EA) to give methyl 1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1, 6-dihydropyridine-3-carboxylate (150 mg, 63%) as a white solid. LRMS ($M+H^+$) m/z calculated 369, found 369.



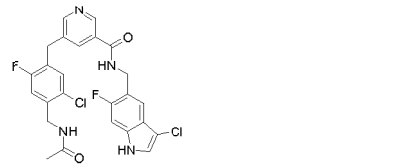
To a mixture of methyl 1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (150 mg, 0.41 mmol, 1.0 eq) in THF/water (2 mL/2mL) was added $LiOH.H_2O$ (26 mg, 0.61 mmol, 1.5 eq). The reaction mixture was kept stirring for 2 h and the mixture was acidified to pH = 6 with 1 N HCl, and concentrated to give 180 mg of crude 1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-

1,6-dihydropyridine-3-carboxylic acid, which was used directly for the next step. LRMS ($M+H^+$) m/z calculated 355, found 355.

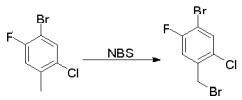


To a solution of 1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl) methyl)benzyl)-6-oxo-1,6-dihydro pyridine-3-carboxylic acid (200 mg, crude) in DMF (5 mL) was added C-(3-chloro-6-fluoro-1H-indol -5-yl)-methylamine hydrochloride (76 mg, 0.41 mmol, 1.0 eq) followed by EDCI (92 mg, 0.48 mmol, 1.2 eq), HOBT (65 mg, 0.48 mmol, 1.2 eq) and TEA (124 mg, 1.23 mmol, 3.0 eq). The reaction mixture was heated to 40 °C and kept stirring for overnight. LRMS showed the SM was consumed. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (15 mg, 7%) as a white solid. LRMS ($M+H^+$) m/z calculated 535, found 535. ^1H NMR (CD_3OD, 400 MHz) δ 8.39 (d, 1 H), 7.98 (d, 1 H), 7.68 (d, 1 H), 7.51-7.55 (m, 2 H), 7.25-7.30 (m, 2 H), 7.12-7.18 (m, 3 H), 6.54-6.60 (m, 2 H), 6.38-6.42 (t, 1 H), 5.27 (s, 4 H), 4.67 (s, 2 H).

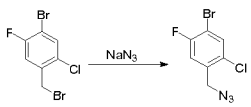
Example 187: Preparation of 5-(4-(acetamidomethyl)-5-chloro-2-fluorobenzyl)-N-((3-chloro-6-fluoro -1H-indol-5-yl)methyl)nicotinamide



5-(4-(acetamidomethyl)-5-chloro-2-fluorobenzyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)nicotinamide

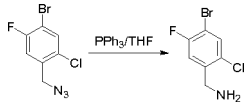


The mixture of 1-bromo-5-chloro-2-fluoro-4-methyl-benzene (10.0 g, 44.75 mmol, 1.0 eq), NBS (7.9 g, 44.75 mmol, 1.0 eq) and AIBN (736 mg, 4.48 mmol, 0.1 eq) in CCl_4 (250 mL) was heated to reflux and kept stirring for 3 h under N_2. The mixture was concentrated. The residue was purified by column chromatography (PE~PE/EA = 30/1, v/v) to give 1-bromo-4-bromomethyl-5-chloro-2-fluoro-benzene (7.5 g, 56%) as a yellow oil.

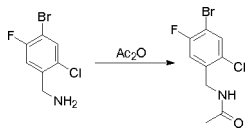


To the mixture of 1-bromo-4-bromomethyl-5-chloro-2-fluoro-benzene (7.5 g, 24.81 mmol, 1.0 eq) in DMF (50 mL) was added NaN_3 (1.9 g, 29.77 mmol, 1.2 eq) at 0 °C and then the resultant mixture was warmed to rt and kept stirring for 2 h. EA (80 mL) was added. The mixture was washed with brine, and the organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography

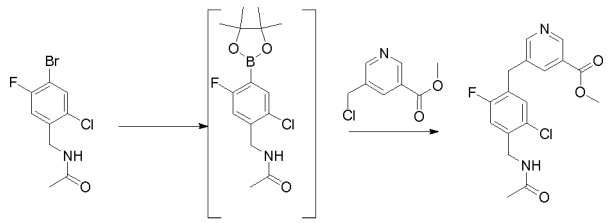
(PE~PE/EA = 30/1, v/v) to give1-azidomethyl-4-bromo-2- chloro-5-fluoro-benzene (6 g, crude) as a yellow oil, which was used directly without further purification.



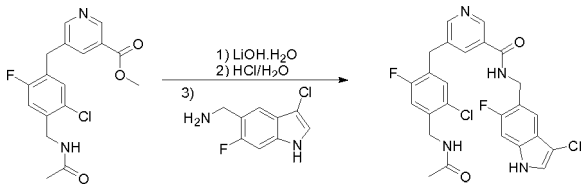
To a solution of 1-azidomethyl-4-bromo-2- chloro-5-fluoro-benzene (4 g, 15.15 mmol, 1.0 eq) in THF (20 mL) and water (5 mL) was added PPh_3 (5.9 g, 22.73 mmol, 1.5 eq) at 0 ºC, and then the resultant mixture was warmed to rt and kept stirring for 4 h. The reaction mixture was concentrated and the residue was purified by column chromatography on a silica gel (DCM/MeOH = 10/1, v/v) to give 4-bromo-2-chloro -5-fluoro-benzylamine (1.8 g, 50%) as a yellow solid. LRMS ($M+H^+$) m/z calculated 238, 240, found 238, 240.



N-(4-bromo-2- chloro-5-fluoro-benzyl)-acetamide (1.6 g, 76%) was prepared as described for 5-[4-(acetylamino-methyl)-2-fluoro-benzyl]-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 280, 282 found 280, 282.

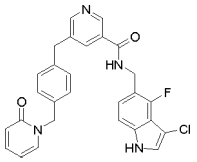


5-[4-(Acetylamino-methyl)-5-chloro-2-fluoro-benzyl]-nicotinic acid methyl ester (550 mg, 46%) was prepared as described for 5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3- ylmethyl]-nicotinic acid methyl ester as a yellow solid. LRMS ($M+H^+$) m/z calculated 351, found 351.



5-(4-(Acetamidomethyl)-5-chloro-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide (45 mg, 30%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 517, found 517. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.39 (br, 1 H), 9.18 (t, 1 H), 8.91 (d, 1 H), 8.64 (d, 1 H), 8.34 (t, 1 H), 8.05 (s, 1 H), 7.50-7.53 (d, 2 H), 7.45 (d, 1 H), 7.22 (d, 2 H), 7.13 (d, 1 H), 4.59 (d, 2 H), 4.25 (d, 2 H), 4.05 (s, 2 H), 1.89 (s, 3 H).

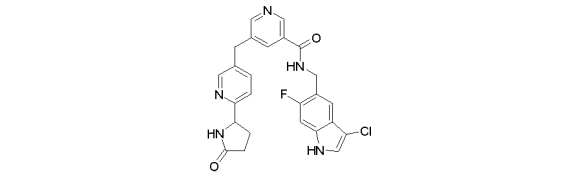
Example 188: Preparation of N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide



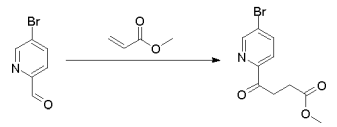
N-((3-chloro-4-fluoro-1*H*-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl) methyl)benzyl)nicotinamide

N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide (20 mg, 13%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 501, found 501. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.57 (br, 1 H), 9.11 (t, 1 H), 8.86 (d, 1 H), 8.60 (d, 1 H), 8.04 (t, 1 H), 7.72-7.75 (m, 1 H), 7.50 (d, 1 H), 7.36-7.42 (m, 1 H), 7.11-7.25 (m, 6 H), 6.37-6.40 (m, 1 H), 6.18-6.22 (m, 1 H), 5.04 (s, 2 H), 4.56 (d, 2 H), 3.99 (s, 2 H).

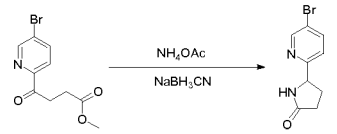
Example 189: Preparation of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide



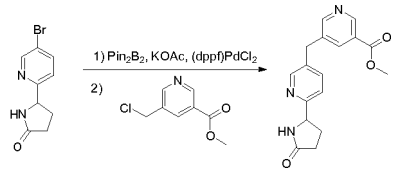
N-(3-Chloro-6-fluoro-1*H*-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide



To a solution of 5-bromo-pyridine-2-carbaldehyde (2.82 g, 20 mmol, 1.0 eq) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (1.0 g, 4.0 mmol, 0.2 eq) in dry MeOH (100 mL) was added methyl acrylate (2.2 mL, 24 mmol, 1.2 eq) and Et_3N (8.4 mL, 60 mmol, 3 eq). The mixture was stirred at 70 °C for 1 h. After cooling to rt, the mixture was quenched with saturated NH_4Cl solution. MeOH was removed by evaporation. The aqueous layer was extracted with EA. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (PE/EA = 50/1, v/v) to afford 4-(5-bromo-pyridin-2-yl)-4-oxo-butyric acid methyl ester (1.6 g, 30%) as a yellow solid.

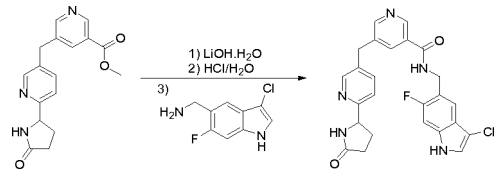


To a solution of 4-(5-bromo-pyridin-2-yl)-4-oxo-butyric acid methyl ester (840 mg, 3.1 mmol, 1.0 eq) in MeOH (15 mL) was added NH_4OAc (2.4 g, 31 mmol, 10 eq). The mixture was stirred at rt for 1 h, then $NaBH_3CN$ (215 mg, 3.41 mmol, 1.1 eq) was added and the reaction mixture was stirred at refluxing for 4 h. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was dissolved in EA and washed with water. The organic phase was dried and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (EA) to afford 5-(5-bromo-pyridin-2-yl)-pyrrolidin-2-one (390 mg, 52%) as a white solid.



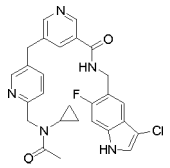
To a solution of 5-(5-bromo-pyridin-2-yl)-pyrrolidin-2-one (390 mg, 1.63 mmol, 1 eq) and $B_2(Pin)_2$ (413 mg, 1.63 mmol, 1 eq) in dioxane (10 mL) was added KOAc (478 mg, 4.88 mmol, 3 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (66 mg, 0.08 mmol, 0.05 eq). The mixture was stirred at 95 °C for 30 h. After cooling to rt, 5-chloromethyl-

nicotinic acid methyl ester (363 mg, 1.96 mmol, 1.2 eq), $Pd(dppf)Cl_2.CH_2Cl_2$ (66 mg, 0.08 mmol, 0.05 eq), Na_2CO_3 (517 mg, 4.88 mmol, 3 eq) and water (3 mL) was added to the mixture. The mixture was stirred at 90 °C for 1 h under nitrogen atmosphere. After cooling to rt, the solvent was removed in vacuo. The residue was purified by chromatography on a silica gel column (DCM/MeOH = 20/1, v/v) to afford 5-[6-(5-Oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinic acid methyl ester (130 mg, 26%) as a yellow solid.



To a solution of 5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinic acid methyl ester (130 mg, 0.42 mmol, 1.0 eq) in THF (5 mL)/H_2O (5 mL) was added $LiOH.H_2O$ (20 mg, 0.46 mmol, 1.1 eq). The mixture was stirred at 40 °C for 1 h and was acidified to pH = 5 with 1 N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification. To a solution of the above crude product and C-(3-chloro-6-fluoro-1H-indol-5-yl)-methylamine (117 mg, 0.51 mmol, 1.2 eq) in DMF (8 mL) was added HATU (194 mg, 0.51 mmol, 1.2 eq) and Et_3N (0.18 mL, 1.25 mmol, 3 eq). The mixture was stirred at rt for 1 h and diluted with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/MeOH = 10/1, v/v) to give N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin- 3-ylmethyl]-nicotinamide (60 mg, 30% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 478.1, found 478.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.87 (d, 1 H), 8.60 (d, 1 H), 8.47 (d, 1 H), 8.10 (t, 1 H), 7.69 (dd, 1 H), 7.53 (d, 1 H), 7.35 (d, 1 H), 7.24 (s, 1 H), 7.13 (d, 1 H), 4.85-4.81 (m, 1 H), 4.70 (s, 2 H), 4.10 (s, 2 H), 2.63-2.54 (m, 1 H), 2.45-2.39 (m, 2 H), 2.07-1.98 (m, 1 H).

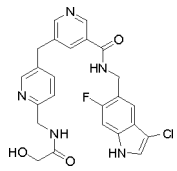
Example 190: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)nicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-5-((6-((*N*-cyclopropyl acetamido)methyl)pyridin-3-yl)methyl)nicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl) methyl)-5-((6-((N-cyclopropyl acetamido)methyl)pyridin-3-yl)methyl)nicotinamide (45 mg, 36%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3- ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 506, found 506. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.39 (br, 1 H), 9.16 (t, 1 H), 8.90 (d, 1 H), 8.66 (d, 1 H), 8.45 (s, 1 H), 8.09 (s, 1 H), 7.60 (d, 1 H), 7.50 (d, 1 H), 7.45 (d, 1 H), 7.22 (d, 1 H), 7.09 (d, 1 H), 4.59 (d, 2 H), 4.51 (s, 1 H), 4.03 (s, 2 H), 2.77-2.81 (m, 1 H), 2.16 (s, 3 H), 1.73-1.75 (m, 4 H).

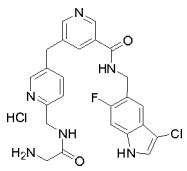
Example 191: Preparation of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-{6-[(2-hydroxy-acetylamino)-methyl]-pyridin-3-ylmethyl}-nicotinamide



N-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-5-{6-[(2-hydroxy-acetylamino)-methyl]-pyridin-3-ylmethyl}-nicotinamide

N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-{6-[(2-hydroxy-acetylamino)-methyl]-pyridin-3-ylmethyl}-nicotinamide (20 mg, 35%) was prepared as described for 5-{4-[(2-amino-acetylamino)-methyl]-2-fluoro-benzyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide as a yellow oil. LRMS ($M+H^+$) m/z calculated 482.1, found 482.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.86 (s, 1 H), 8.57 (s, 1 H), 8.39 (s, 1 H), 8.08 (d, 1 H), 7.60 (d, 1 H), 7.50 (d, 1 H), 7.28-7.22 (m, 2 H), 7.11 (d, 1 H), 4.68 (s, 2 H), 4.51 (s, 2 H), 4.05 (d, 1 H).

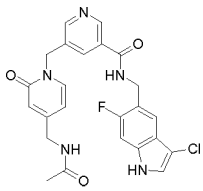
Example 192: Preparation of 5-((6-((2-aminoacetamido)methyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide



5-((6-((2-aminoacetamido)methyl)pyridin-3-yl)methyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)nicotinamide hydrochloride

5-{6-[(2-Amino-acetylamino)-methyl]-pyridin-3-ylmethyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide (40 mg, 59.5%) was prepared as described for 5-(6-aminomethyl-pyridin-3-ylmethyl)-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide as yellow solid. LRMS (M+H+) m/z calculated 481.1, found 481.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.49 (s, 1 H), 9.42 (t, 1 H), 9.24 (t, 1 H), 9.07 (d, 1 H), 8.87 (d, 1 H), 8.78 (d, 1 H), 8.24 (s, 1 H), 7.71 (d, 1 H), 7.52-7.48 (m, 2 H), 7.26-7.23 (m, 1 H), 4.61 (d, 4 H), 4.27 (s, 2 H), 3.71-3.66 (m, 2 H).

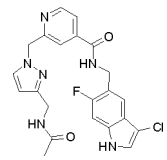
Example 193: Preparation of 5-((4-(acetamidomethyl)-2-oxopyridin-1(2H)-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide



5-((4-(acetamidomethyl)-2-oxopyridin-1(2H)-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide

5-((4-(Acetamidomethyl)-2-oxopyridin-1(2H)-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide (73 mg, 67% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3- ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 428.1, found 428.1. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (t, 1 H), 8.96 (d, 1 H), 8.69 (d, 1 H), 8.32 (t, 1 H), 8.11 (s, 1 H), 7.83 (d, 1 H), 7.51 (d, 1 H), 7.47 (d, 1 H), 7.24 (d, 1 H), 6.23 (s, 1 H), 6.17 (dd, 1 H), 5.14 (s, 2 H), 4.60 (d, 2 H), 4.08 (s, 2 H), 1.88 (s, 3 H).

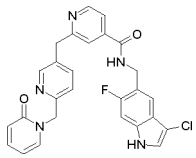
Example 194: Preparation of 2-((3-(acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-((3-(acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

2-((3-(Acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (45 mg, 33% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 455.1, found 455.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.40 (s, 1 H), 9.28 (t, 1 H), 8.68 (d, 1 H), 8.15 (t, 1 H), 7.79 (d, 1 H), 7.72 (d, 1 H), 7.56 (s, 1 H), 7.51 (d, 1 H), 7.45 (d, 1 H), 7.23 (d, 1 H), 6.15 (d, 1 H), 5.42 (s, 2 H), 4.59 (d, 2 H), 4.16 (d, 2 H), 1.80 (s, 3H).

Example 197: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide

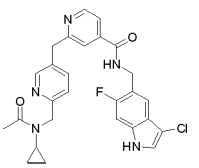


N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-((6-((2-oxopyridin-1(2*H*)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide

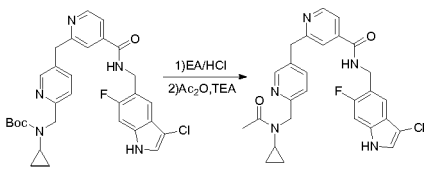
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide (50 mg, 42% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin -3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 502.1, found 502.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.60 (d, 1 H), 8.46 (d, 1 H), 7.74-7.70 (m, 4 H), 7.56-7.53 (m, 2 H), 7.25 (s, 1 H), 7.24 (d, 1 H), 7.14 (d, 1 H), 6.55 (d, 1 H), 6.40 (dt, 1 H), 5.24 (s, 2 H), 4.71 (s, 2 H), 4.22 (s, 2 H).

Example 195, 196, 198, 199, 200 were prepared as described for N-((3-chloro-6-fluoro-1H- indol-5-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide.

Example 201: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide



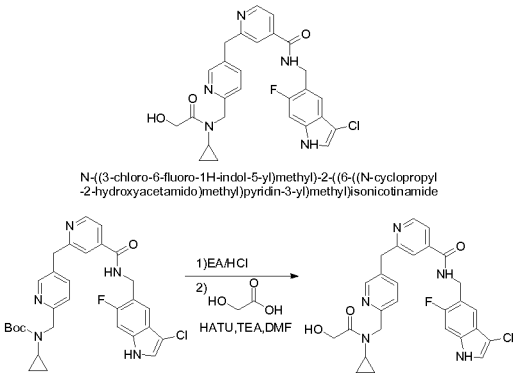
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide



To a solution of (5-{4-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]- pyridin-2-ylmethyl}-pyridin-2-ylmethyl)-cyclopropyl-carbamic acid *tert*-butyl ester (70 mg, 0.12 mmol, 1.0 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 5 h. The mixture was concentrated in vacuo and to this residue in DCM was added Ac_2O (25 mg, 0.24 mmol, 2 eq) and TEA (50 mg, 0.48 mmol, 4 eq). The mixture was stirred at rt for overnight. The mixture was quenched with water. The aqueous layer was extracted with DCM. The

combined extracts were dried and concentrated. The residue was purified by prep-HPLC to give N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl) pyridin-3-yl)methyl)isonicotinamide (27 mg, 43% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 506.1, found 506.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.38 (s, 1 H), 9.22 (t, 1 H), 8.63 (d, 1 H), 8.44 (s, 1 H), 7.75 (s, 1 H), 7.64-7.61 (m, 2 H), 7.51 (d, 1 H), 7.46 (d, 1 H), 7.24 (d, 1 H), 7.11 (d, 1 H), 4.59 (d, 2 H), 4.52 (s, 2 H), 4.15 (s, 2 H), 2.80-2.77 (m, 1 H), 2.17 (s, 3 H), 0.76-0.74 (m, 4 H).

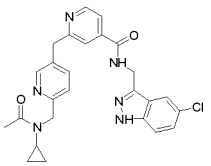
Example 202: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((N-cyclopropyl-2-hydroxyacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((N-cyclopropyl-2-hydroxyacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide

To a suspension of (5-{4-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]- pyridin-2-ylmethyl}-pyridin-2-ylmethyl)-cyclopropyl-carbamic acid *tert*-butyl ester (100 mg, 0.18 mmol, 1.0 eq) in EA was added HCl/EA solution. The mixture was stirred at rt for 5 h. The mixture was concentrated in vacuo and residue in DMF was added hydroxy-acetic acid (16 mg, 0.27 mmol, 1.2 eq), HATU (67 mg, 0.18 mmol, 1.0 eq) and TEA (89 mg, 0.9 mmol, 5 eq). The mixture was stirred at rt for 1 h. The mixture was quenched with water extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by prep-HPLC to give N-((3-chloro-6-fluoro-1H-indol-5-yl)-methyl)-2-((6-((N-cyclopropyl-2-hydroxyacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide (19 mg, 21% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 522.1, found 522.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.23 (t, 1 H), 8.63 (d, 1 H), 8.45 (s, 1 H), 7.75 (s, 1 H), 7.64-7.62 (m, 2 H), 7.50 (s, 1 H), 7.46 (d, 1 H), 7.24 (d, 1 H), 7.14 (d, 1 H), 4.59 (d, 2 H), 4.56 (s, 2 H), 4.45 (t, 1 H), 4.32 (d, 2 H), 4.15 (s, 2 H), 2.72-2.72 (m, 1 H), 0.75-0.70 (m, 4 H).

Example 203: Preparation of N-((5-chloro-1H-indazol-3-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide

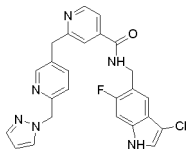


N-((5-chloro-1H-indazol-3-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide

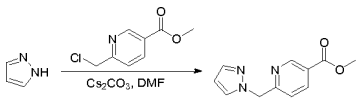
N-((5-chloro-1H-indazol-3-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide (12 mg, 20%) was prepared as described for N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 489.1, found 489.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.09 (s, 1 H), 9.38 (t, 1

H), 8.63 (d, 1 H), 8.44 (s, 1 H), 7.91 (s, 1 H), 7.75 (s, 1 H), 7.62 (d, 2 H), 7.55 (d, 1 H), 7.36 (d, 1 H), 7.11 (d, 1 H), 4.80 (d, 2 H), 4.52 (s, 2 H), 4.15 (s, 2 H), 2.81-2.79 (m, 1 H), 2.18 (s, 3 H), 0.76-0.75 (m, 4 H).

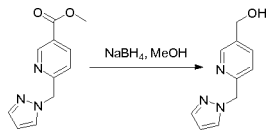
Example 204: Preparation of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(6-pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-isonicotinamide



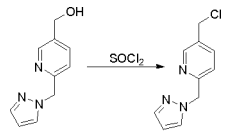
N-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-2-(6-pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-isonicotinamide



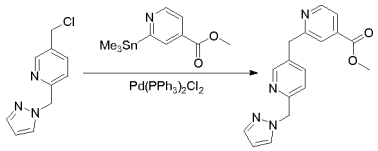
To a solution of 1H-pyrazole (1.4 g, 20.3 mmol, 1.5 eq) in THF (30 mL) was added Cs_2CO_3 (13.2 g, 40.5 mmol, 3.0 eq) and 6-chloromethyl-nicotinic acid methyl ester (2.5 g, 13.0 mmol, 1.0 eq). The reaction mixture was stirred for 1 h at 60 °C. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated to give the crude product which was subject to silica gel chromatography (PE/EA = 3/1~1/1, v/v) to afford 6-pyrazol-1-ylmethyl-nicotinic acid methyl ester (1.9 g, 67%) as a white solid.



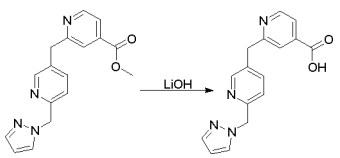
(6-Pyrazol-1-ylmethyl-pyridin-3-yl)-methanol (0.8 g, 50%) was prepared as described for 1-(2-fluoro-4-(hydroxyl methyl)benzyl)pyridin-2(1H)-one as a white solid.



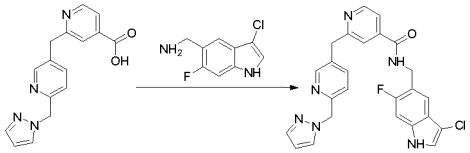
5-Chloromethyl-2-pyrazol-1-ylmethyl-pyridine (0.7 g, 81%) was prepared as described for as 1-(4-chloromethyl-2-methanesulfonyl-benzyl)-1H-pyridin-2-one as a brown solid.



2-(6-Pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-isonicotinic acid methyl ester (180 mg, 40%) was prepared as described for 2-[6-(2-oxo-2*H*-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]-isonicotinic acid methyl ester as a yellow solid.

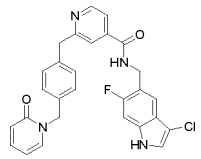


2-(6-Pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-isonicotinic acid (170 mg, crude) was prepared as described for 1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid as a white solid, which was used without purification.



N-(3-chloro-6-fluoro-1h-indol-5-ylmethyl)-2-(6-pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-isonicotinamide (140 mg, 50%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 475.1, found 475.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.21 (t, 1 H), 8.61 (d, 1 H), 8.49 (s, 1 H), 7.82 (d, 1 H), 7.73 (s, 1 H), 7.62-7.66 (m, 2 H), 7.51 (d, 2 H), 7.44-7.45 (m, 2 H), 7.21 (d, 1 H), 6.91 (d,1 H), 6.27 (t, 1 H), 5.38 (s, 2 H), 4.79 (s, 1 H), 4.58 (d, 2 H), 4.16 (s, 2 H).

Example 205: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

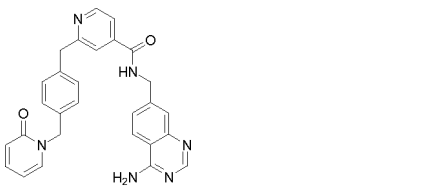


N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-(4-((2-oxopyridin-1(2*H*)-yl)methyl)benzyl)isonicotinamide

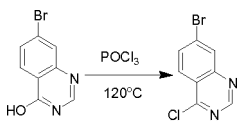
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (40 mg, 27% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 501.1, found 501.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.54 (dd, 1 H), 7.64 (s, 1 H), 7.64-7.58 (m, 2 H), 7.50-7.44 (m, 2 H), 7.22-7.20 (m, 5 H), 7.10 (d, 1 H), 6.52 (d, 1 H), 6.32 (t, 1 H), 5.11 (s, 2 H), 4.66 (s, 2 H), 4.13 (s, 2 H).

Example 206, 207, 211, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, and 332 were prepared as described for N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide.

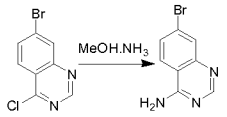
Example 208: Preparation of N-((4-aminoquinazolin-7-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



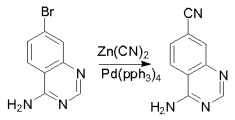
N-((4-aminoquinazolin-7-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



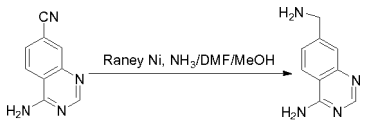
To a solution of 7-bromo-quinazolin-4-ol (10 g, 44.4 mmol, 1.0 eq) in $POCl_3$ (200 mL). The mixture was stirred at 120 °C for overnight. The mixture was concentrated and extracted with DCM and the combined extracts were washed with brine, dried and concentrated to give 7-bromo-4-chloro-quinazoline as a yellow solid (10 g, crude).



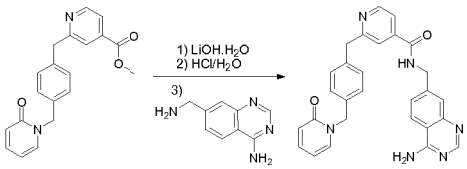
To a solution of 7-bromo-4-chloro-quinazoline (10 g, 41.50 mmol, 1.0 eq) in MeOH/NH_3 (500 mL) and was stirred at 30 °C for 48 h. The mixture was concentrated to give 7-bromo-quinazolin-4-ylamine as a yellow solid (10 g, crude).



To a solution of 7-bromo-quinazolin-4-ylamine (10 g, 45.04 mmol, 1.0 eq) in DMF (400 mL) was added $Zn(CN)_2$ (13.22 g, 112.3 mmol, 2.5 eq) and $Pd(pph_3)_4$ (5.2 g, 4.51 mmol, 0.1 eq). The mixture was stirred at 120 °C for 4 h. The mixture was concentrated and extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/MeOH = 50/1, v/v) to give 4-amino-quinazoline-7-carbonitrile (4.5 g, 59%) as a yellow oil.

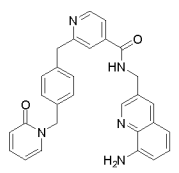


To a solution of 4-amino-quinazoline-7-carbonitrile (4.5 g, 26.47 mmol, 1 eq) in MeOH (200 mL), DMF (200 mL) and ammonium hydroxide (100 mL) was added Raney Ni (4.0 g). The mixture was stirred at 40 °C overnight under hydrogen atmosphere. Raney Ni was filtered off and the filtrate was concentrated in vacuo to give 7-aminomethyl-quinazolin-4-ylamine (3 g, crude) as a yellow solid.

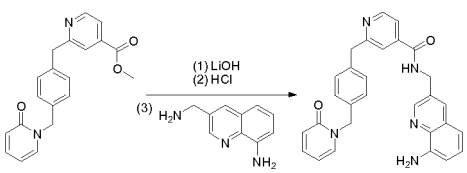


N-((4-aminoquinazolin-7-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (15 mg, 13% yield for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as an off-white solid. LRMS ($M+H^+$) m/z calculated 577.1, found 577.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.42 (t, 1 H), 8.63-8.64 (d, 1 H), 8.36 (s, 1 H), 8.15-8.17 (d, 1 H), 7.64-7.76 (m, 5 H), 7.54 (s, 1 H), 7.41-7.43 (m, 2 H), 7.20-7.27 (m, 4 H), 6.38-6.40 (d, 1 H), 6.21 (t, 1 H), 5.04 (s, 2 H), 4.61-4.63 (d, 2 H), 4.13 (s, 2 H).

Example 209: Preparation of N-((8-aminoquinolin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

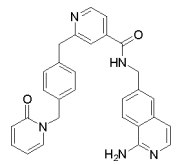


N-((8-aminoquinolin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



To a solution of 2-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinic acid methyl ester (162 mg, 0.49 mmol, 1.0 eq) in THF (3 mL)/H_2O (2 mL) was added LiOH.H_2O (25 mg, 0.58 mmol, 1.2 eq). The mixture was stirred at 40 °C for 1 h and was acidified to pH = 5 with 1 N HCl solution. The mixture was concentrated in vacuo and the residue was directly used without further purification. To a solution of the above crude product and 3-aminomethyl-quinolin-8-ylamine (102 mg, 0.49 mmol, 1.0 eq) in DMF (5 mL) was added HOBT (99 mg, 0.73 mmol, 1.5 eq), EDCI (140 mg, 0.73 mmol, 1.5 eq) and Et_3N (148 mg, 1.46 mmol, 3 eq). The mixture was stirred at rt for 12 h and concentrated. The residue was purified by prep-HPLC to give N-((8-aminoquinolin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (15 mg, 6.5% yields for 2 steps) as a white solid. LRMS ($M+H^+$) m/z calculated 476.2, found 476.2. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.39 (t, 1 H), 8.71 (d, 1 H), 8.63 (d, 1 H), 8.03 (s, 1 H), 7.75 (d, 1 H), 7.70 (s, 1 H), 7.63 (d, 1 H), 7.42 (t, 1 H), 7.36-7.19 (m, 5 H), 7.04 (d, 1 H), 6.84 (s, 1 H), 6.40 (s, 1 H), 6.20 (t, 1 H), 5.04 (s, 2 H), 4.65 (d, 2 H), 4.12 (s, 2 H).

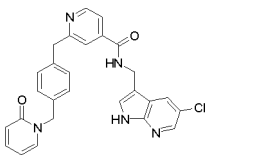
Example 210: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (25 mg, 18% yields for 2 steps) was prepared as described for N-((8-aminoquinolin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide as an off-white solid. LRMS ($M+H^+$) m/z calculated 476.2, found 476.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.59 (d, 1 H), 8.09 (d, 1 H), 7.73-7.62 (m, 5 H), 7.48 (d, 1 H), 7.46 (d, 1 H), 7.23 (s, 4 H), 6.94 (d, 1 H), 6.55 (d, 1 H), 6.36 (d, 1 H), 5.13 (s, 2 H), 4.70 (s, 2 H), 4.17 (s, 2 H).

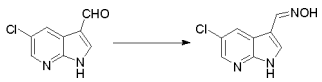
Example 212: Preparation of N-((5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



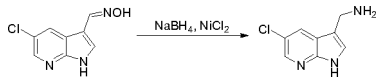
N-((5-chloro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



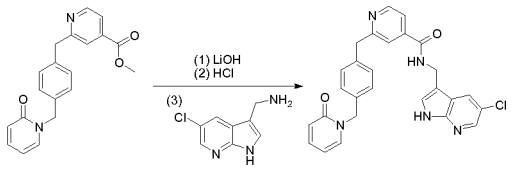
To a suspension of 5-chloro-1H-pyrrolo[2,3-b]pyridine (10.0 g, 65.5 mmol, 1 eq) in AcOH (56.7 mL) and water (28.3 mL) was added hexamethylenetetramine (11.9 g, 85.2 mmol, 1.3 eq). The mixture was stirred under reflux overnight, followed by addition of 200 mL of water. After stirring for 30 min, the reaction mixture was filtered to recover the solid, then dried under air to give 5-cloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (6.2 g, 53%) as a yellow solid.



To a solution of 5-cloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (1.0 g, 5.55 mmol, 1 eq) in EtOH (40 mL) and water (10 mL) was added hydroxylammonium chloride (575 mg, 8.33 mmol, 1.5 eq) and Na_2CO_3 (1.06 g, 10.0 mmol, 1.8 eq). The mixture was stirred under reflux for 3 h and then cooled to rt. The precipitate was collected by filtration to give 5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde oxime (1.0 g, 92%) as an off white solid.

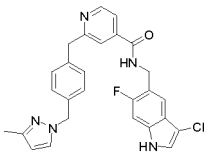


To a solution of 5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde oxime (200 mg, 2 mmol, 1 eq) in MeOH (5 mL) was added $NiCl_2$ (128 mg, 1 mmol, 1 eq) and $NaBH_4$ (228 mg, 6 mmol, 6 eq). The mixture was stirred at rt for 5 h under hydrogen atmosphere. $NiCl_2$ was filtered off and the filtrate was concentrated in vacuo to give C-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-methylamine (65 mg, 30%) as a yellow solid.

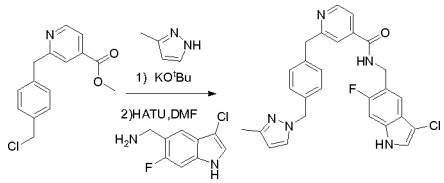


N-((5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (49 mg, 34% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 484.2, found 484.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.76 (s, 1 H), 9.13 (t, 1 H), 8.59 (d, 1 H), 8.18 (dd, 1 H), 7.75 (d, 1 H), 7.66 (s, 1 H), 7.57 (d, 1 H), 7.52 (d, 1 H), 7.42-7.36 (m, 1 H), 7.25-7.18 (m, 4 H), 6.40 (d, 1 H), 6.20 (t, 1 H), 5.03 (s, 2 H), 4.57 (s, 2 H), 4.09 (s, 2 H).

Example 223: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide



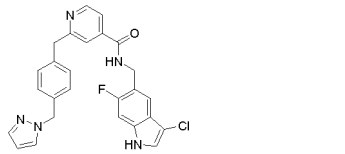
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide



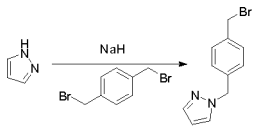
To a solution of 2-(4-chloromethyl-benzyl)-isonicotinic acid methyl ester (100 mg, 0.36 mmol, 1 eq) and 3-methyl-1H-pyrazole (90.72 mg, 1.8 mmol, 3 eq) in THF (5 mL) /DMF (2 mL) was added KO^{t}Bu (79.92 mg, 0.72 mmol, 2 eq). The mixture was stirred at rt for overnight. The mixture was concentrated in vacuo and the residue was directly used without further purification. To a solution of the above crude product and C-(3-chloro-6-fluoro-1H-indol-5-yl)-methylamine (102 mg, 0.43 mmol, 1.2 eq) in DMF (5 mL) was added HATU (136.8 mg, 0.36 mmol, 1.0 eq) and Et_3N (0.19 mg, 1.44 mmol, 4 eq). The mixture was stirred at rt for overnight and concentrated. The residue was purified by prep-HPLC to give N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide (10 mg, 6% yields for 2 steps)

as a white solid. LRMS (M+H$^+$) m/z calculated 488.1, found 488.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.21 (t, 1 H), 8.61-8.60 (d, 1 H), 7.69 (s, 1 H), 7.63-7.61 (m, 2 H), 7.50 (s, 1 H), 7.45-7.43 (d, 1 H), 7.24-7.21 (m, 3 H), 7.13-7.11 (d, 1 H), 7.02-7.00 (d, 1 H), 6.03-5.99 (m, 1 H), 5.22-5.15 (d, 2 H), 4.10 (s, 2 H), 4.60-4.58 (d, 2 H), 4.58-4.57 (d, 2 H), 4.11-4.08 (m, 2 H), 2.17-2.11 (d, 2 H).

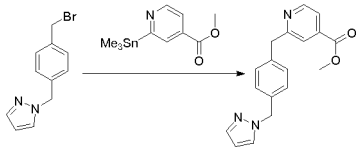
Example 224: Preparation of N-(3-chloro-6-fluoro-1h-indol-5-ylmethyl)-2-(4-pyrazol-1-ylmethyl-benzyl)-isonicotinamide



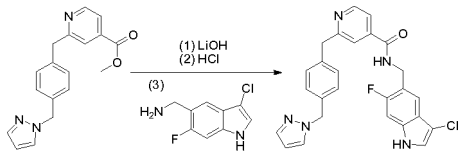
N-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-2-(4-pyrazol-1-ylmethyl-benzyl)-isonicotinamide



To a solution of 1H-pyrazole (0.52 g, 7.58 mmol, 1.0 eq) in THF (30 mL) was added NaH (0.18 g, 7.58 mmol, 1.0 eq) and 1,4-bis-bromomethyl-benzene (3.0 g,11.36 mmol, 1.5 eq). The reaction mixture was stirred at rt for 1 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated to give the crude product which was subject to silica gel chromatography (PE/EA = 3/1~1/1, v/v) to afford 1-(4-bromomethyl-benzyl)-1H-pyrazole (1.5 g, 79%) as a white solid.

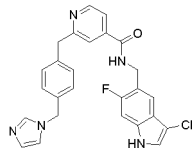


2-(4-Pyrazol-1-ylmethyl-benzyl)-isonicotinic acid methyl ester (130 mg, 21%) was prepared as described for 2-[6-(2-oxo-2*H*-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]-isonicotinic acid methyl ester as a white solid.



N-(3-chloro-6-fluoro-1h-indol-5-ylmethyl)-2-(4-pyrazol-1-ylmethyl-benzyl)-isonicotinamide (30 mg, 15.1%) was prepared as described for N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide as a white solid. LRMS (M+H+) m/z calculated 474.1, found 474.1. ^{1}H NMR (MeOD, 400 MHz) δ 8.59 (d, 1 H), 7.63-7.68 (m, 3 H), 7.50-7.54 (m, 2 H), 7.28 (s, 1 H), 7.26 (s, 2 H), 7.13-7.18 (m, 3 H), 6.32 (t, 1 H), 5.32 (s, 2 H), 5.15 (s, 1 H), 4.71 (s, 2 H), 4.20 (s, 2 H).

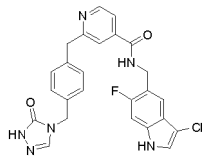
Example 225: Preparation of 2-(4-((1H-imidazol-1-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-(4-((1H-imidazol-1-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

2-(4-((1H-Imidazol-1-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (20 mg, 12% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a off-white solid. LRMS ($M+H^+$) m/z calculated 474.1, found 474.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.23-9.20 (t, 1 H), 8.61-8.60 (d, 1 H), 7.95-7.91 (m, 1 H), 7.69 (s, 1 H), 7.63-7.61 (d, 1 H), 7.51-7.50 (d, 1 H), 7.45-7.44 (d, 1 H), 7.28-7.17 (m, 6 H), 6.89 (s, 1 H), 5.16 (s, 2 H), 4.58-4.57 (d, 2 H), 4.12 (s, 2 H).

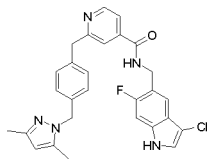
Example 226: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((5-oxo-1H-1,2,4-triazol-4(5H)-yl)methyl)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((5-oxo-1H-1,2,4-triazol-4(5H)-yl)methyl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((5-oxo-1H-1,2,4-triazol-4(5H)-yl)methyl)benzyl)isonicotinamide (17 mg, 11% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a yellow solid. LRMS ($M+H^+$) m/z calculated 491.1, found 491.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.67 (s, 1 H), 11.39 (s, 1 H), 9.21 (t, 1 H), 8.62-8.60 (d, 1 H), 7.91 (s, 1 H), 7.70 (s, 1 H), 7.62-7.61 (d, 1 H), 7.51-7.50 (d, 1 H), 7.46-7.44 (d, 1 H), 7.28-7.18 (m, 5 H), 4.67 (s, 2 H), 4.59-4.57 (d, 2 H), 4.12 (s, 2 H).

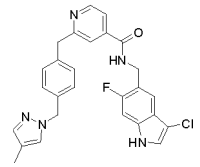
Example 227: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide (8 mg, 5% yields for 2 steps) was prepared as described for N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 502.1, found 502.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.40 (s, 1 H), 9.22 (t, 1 H), 8.62-8.61 (d, 1 H), 7.69 (s, 1 H), 7.63-7.62 (d, 1 H), 7.52-7.51 (d, 1 H), 7.46-7.44 (d, 1 H), 7.25-7.22 (m, 3 H), 7.03-7.01 (d, 2 H), 5.82 (s, 1 H), 5.12 (s, 2 H), 4.59-4.58 (d, 2 H), 4.12 (s, 2 H), 2.14 (s, 3 H), 2.08 (s, 3 H).

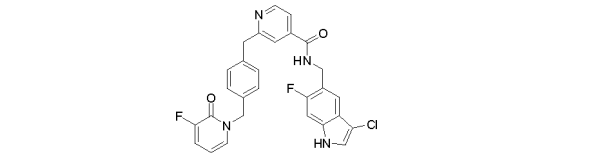
Example 228: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide



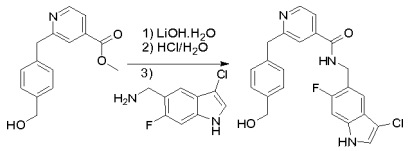
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide (66 mg, 37% yields for 2 steps) was prepared as described for N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 588.1, found 588.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.43 (d, 1 H), 9.35 (d, 1 H), 8.72-8.71 (d, 1 H), 7.85-7.70 (m, 2 H), 7.51-7.45 (m, 3 H), 7.27-7.13 (m, 6 H), 5.50-5.48 (d, 2 H), 4.60 (d, 2 H), 4.20 (s, 2 H), 1.97 (s, 3 H).

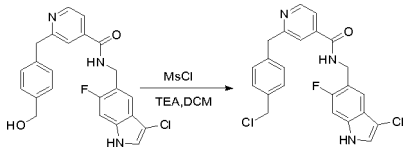
Example 229: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



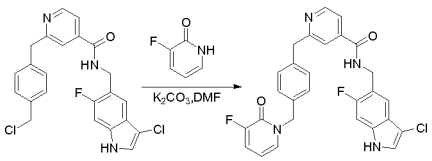
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(4-hydroxymethyl-benzyl)-isonicotinamide (6 g, 91%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a yellow solid.



To a solution of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(4-hydroxymethyl-benzyl)-isonicotinamide (4 g, 9.4 mmol, 1 eq) in DCM (100 mL) was added TEA (3.2 mL, 23.5 mmol, 2.5.0 eq) and MsCl (1.2 g, 11.28 mmol, 1.2 eq). The mixture was stirred at rt for overnight and diluted with water. The mixture was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by chromatography on a silica gel column (DCM/MeOH = 100/1, v/v) to give N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(4-chloromethyl-benzyl)-isonicotinamide (2 g, 48%) as a yellow solid.

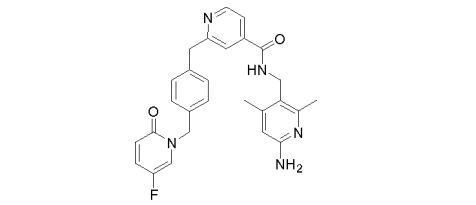


N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (25 mg, 21%) was prepared as described for 3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate as an off-white solid. LRMS ($M+H^+$) m/z calculated 519.1, found 519.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.41 (s, 1 H), 9.25-9.23 (t, 1 H), 8.63-8.62 (d, 1 H), 7.72 (s, 1 H), 7.65-7.63 (m, 2

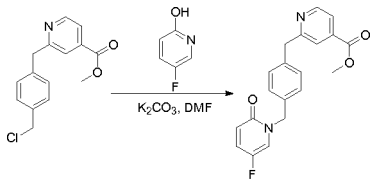
H), 7.52-7.46 (m, 2 H), 7.40-7.35 (m, 1 H), 7.29-7.22 (m, 5 H), 6.23-6.18 (m, 1 H), 5.13 (s, 2 H), 4.61-4.60 (d, 2 H), 4.13 (s, 2 H).

Example 232, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244 were prepared as N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide.

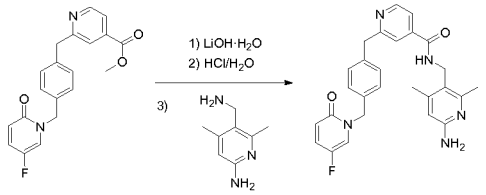
Example 230: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

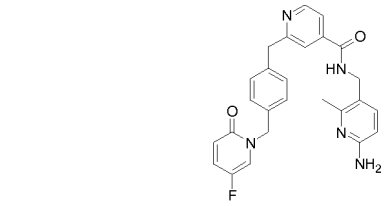


To a solution of 2-(4-chloromethyl-benzyl)-isonicotinic acid methyl ester (1.1 g, 3.99 mmol, 1.0 eq) and 5-fluoro-pyridin-2-ol (0.68 g, 5.99 mmol, 1.5 eq) in DMF (35 mL) was added K_2CO_3 (1.1 g, 7.98 mmol, 2 eq). The mixture was stirred at rt overnight, then concentrated in *vacuum* and the residue was diluted with EA and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (PE/EA= 1/1, v/v) to get N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (1.02 g, 72.8%) as an off white solid.

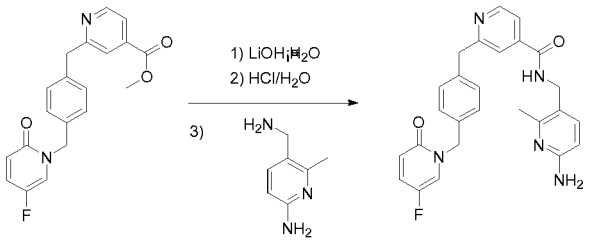


To a solution of 2-[4-(5-fluoro-2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinic acid methyl ester (100 mg, 0.284 mmol, 1.0 eq) in THF (10 mL)/H_2O (2 mL) was added LiOH·H_2O (14.3 mg, 0.341 mmol, 1.2 eq). The mixture was stirred at 40 °C for 1 h and was acidified to pH 5~6 with 1 N HCl solution. The mixture was concentrated in vacuum and the residue was directly used without further purification. To a solution of the crude product and 5-aminomethyl-4,6-dimethyl-pyridin-2-ylamine (63.6 mg, 0.284 mmol, 1.0 eq) in DMF (8 mL) were added HATU (162 mg, 0.426 mmol, 1.5 eq) and Et_3N (115 mg, 1.136 mmol, 4 eq). The mixture was stirred at rt for 4 h then concentrated and the residue was purified by prep-HPLC to give N-(6-amino-2,4-dimethyl-pyridin-3-ylmethyl)-2-[4-(5-fluoro-2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinamide (45 mg, 33.6%) as an off white solid. LCMS ($M+H^+$) m/z calculated 472.2, found 472.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.60 (t, 1 H), 8.56 (d, 1 H), 8.00-8.02 (m, 1 H), 7.66 (s, 1 H), 7.53-7.58 (m, 2 H), 7.24 (t, 4 H), 6.42-6.45 (m, 1 H), 6.13 (s, 1 H), 5.68 (s, 2 H), 4.99 (s, 2 H), 4.34 (d, 2 H), 4.10 (s, 2 H), 2.30 (s, 3 H), 2.17 (s, 3 H).

Example 231: Preparation of N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

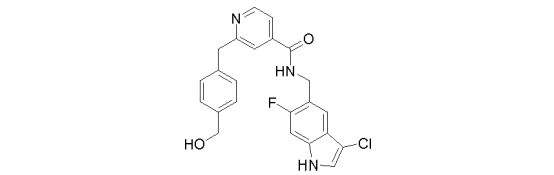


N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

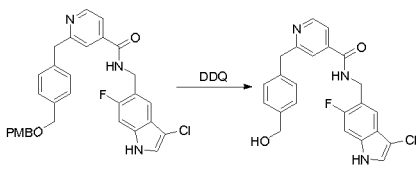


To a solution of 2-[4-(5-fluoro-2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinic acid methyl ester (100 mg, 0.284 mmol, 1.0 eq) in THF (10 mL)/ H_2O (2 mL) was added $LiOH \cdot H_2O$ (14.3 mg, 0.341 mmol, 1.2 eq). The mixture was stirred at 40 ºC for 1 h and was acidified to pH 5~6 with 1 N HCl solution. The mixture was concentrated in vacuum and the residue was directly used without further purification. To a solution of the crude product (95.6 mg, 0.284 mmol, 1.0 eq) and 5-aminomethyl-6-methyl-pyridin-2-ylamine (59 mg, 0.284 mmol, 1.0 eq) in DMF (8 mL) were added HATU (162 mg, 0.426 mmol, 1.5 eq) and Et_3N (115 mg, 1.136 mmol, 4 eq). The mixture was stirred at rt for 4 h then concentrated and the residue was purified by prep-HPLC to give N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (65 mg, 50%) as an off-white solid. LCMS ($M+H^+$) m/z calculated 458.2, found 458.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.95 (t, 1 H), 8.58 (d, 1 H), 8.01 (d, 1 H), 7.67 (s, 1 H), 7.55-7.59 (m, 2 H), 7.24 (t, 5 H), 6.41-6.45 (m, 1 H), 6.23 (d, 1 H), 5.72 (s, 2 H), 4.99 (s, 2 H), 4.28 (d, 2 H), 4.10 (s, 2 H), 2.27 (s, 3 H).

Example 233: Preparation of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(4-hydroxymethyl-benzyl)-isonicotinamide



N-(3-Chloro-6-fluoro-1*H*-indol-5-ylmethyl)-2-(4-hydroxymethyl-benzyl)-isonicotinamide

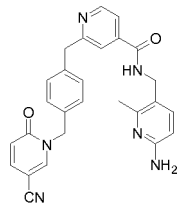


To a solution of compound N-[(3-chloro-6-fluoroindol-5-yl)methyl]{2-[(4-{[(4-methoxyphenyl)methoxy]methyl}phenyl)methyl](4-pyridyl)}carboxamide (0.62 g, 1.14 mmol, 1 eq) in DCM/H_2O (18 mL/1 mL) was added DDQ (0.41g, 1.82 mmol, 1.6 eq). The mixture was stirred at rt for 0.5 h. The mixture was diluted with EA and water. The organic layer was separated and the aqueous layer was extracted with EA. The combined organic layers were dried and concentrated. The residue was purified by

chromatography on a silica gel column (PE/EA = 1/1, v/v) to give N-[(3-chloro-6-fluoroindol-5-yl)methyl](2-{[4-(hydroxymethyl)phenyl]methyl}(4-pyridyl))carboxamide (12 mg, 25%) as a white solid. LRMS (M+H+) m/z calculated 424.2, found 424.1.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.20-9.23 (t, 1 H), 8.62-8.63 (d, 1 H), 7.70 (s, 1 H), 7.62-7.63 (d, 1 H), 7.44-7.50 (m, 2 H), 7.21-7.24 (m, 5H), 5.07-5.10 (m, 1 H), 4.57-4.59 (d, 2 H), 4.42-4.44 (d, 2 H), 4.14 (s, 2 H).

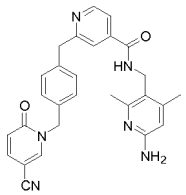
Example 245: Preparation of N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (110 mg, 28.3%) was prepared as described for N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS (M+H$^+$) m/z calculated 465.2, found 465.2. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.58 (d, 1 H), 8.48 (d, 1 H), 7.60-7.66 (m, 3 H), 7.41 (d, 1 H), 7.31 (dd, 4 H), 6.59 (d, 1 H), 6.42 (d, 1 H), 5.17 (s, 2 H), 4.44 (s, 2 H), 4.20 (s, 2 H).

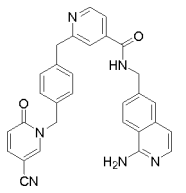
Example 246: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



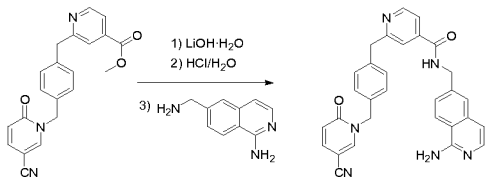
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (270 mg, 40.5%) was prepared as described for N-(6-amino-2,4-dimethyl-pyridin-3-ylmethyl)-2-[4-(5-fluoro-2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinamide as an off-white solid. LRMS (M+H$^+$) m/z calculated 478.9, found 478.9. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.77 (d, 1 H), 8.54-8.61 (m, 2 H), 7.65-7.69 (m, 2 H), 7.55-7.57 (m, 1 H), 7.25 (s, 4 H), 6.49 (d, 1 H), 6.11 (s, 1 H), 5.67 (s, 2 H), 5.04 (d, 2 H), 4.33 (d, 2 H), 4.10 (d, 2 H), 2.29 (s, 3 H), 2.15 (s, 3 H).

Example 247: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

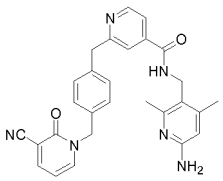


N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



To a solution of 2-[4-(5-cyano-2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinic acid methyl ester (100 mg, 0.278 mmol, 1.0 eq) in THF (10 mL)/H_2O (2 mL) was added LiOH·H_2O (15 mg, 0.334 mmol, 1.2 eq). The mixture was stirred at 40 °C for 2 h and was acidified to pH 5~6 with 1 N HCl solution. The mixture was concentrated in *vacuum* and the residue was directly used without further purification. To a solution of the crude product and 5-aminomethyl-4,6-dimethyl-pyridin-2-ylamine (62.2 mg, 0.278 mmol, 1.0 eq) in DMF (8 mL) were added HOBT (56.4 mg, 0.418 mmol, 1.5 eq), EDCI (80 mg, 0.418 mmol, 1.5 eq) and Et_3N (113 mg, 1.114 mmol, 4 eq). The mixture was stirred at 40 °C for 4 h, then concentrated and the residue was purified by prep-HPLC to give N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (17 mg, 12.2%) as a yellow solid. LRMS ($M+H^+$) m/z calculated 500.9, found 500.9. ^1H NMR (CD_3OD, 400 MHz) δ 8.46 (d, 1 H), 8.30 (d, 1 H), 7.94 (d, 1 H), 7.58-7.60 (m, 2 H), 7.52 (dd, 1 H), 7.49 (s, 1 H), 7.45 (dd, 1 H), 7.35 (dd, 1 H), 7.15 (dd, 4 H), 6.81 (d, 1 H), 6.41 (d, 1 H), 5.00 (s, 2 H), 4.58 (s, 2 H), 4.06 (s, 2 H), 3.20-3.21 (m, 2 H).

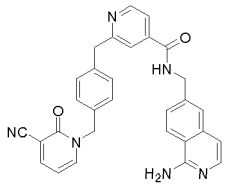
Example 248: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (15 mg, 11.2%) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 478.9, found 478.9. ^1H NMR (CD_3OD, 400 MHz) δ 8.42 (d, 1 H), 7.91 (d, 2 H), 7.50 (s, 1 H), 7.44 (dd, 1 H), 7.14 (dd, 4 H), 6.33 (t, 1 H), 6.19 (s, 1 H), 5.05 (s, 2 H), 4.38 (s, 2 H), 4.04 (s, 2 H), 2.27 (s, 3 H), 2.14 (s, 3 H).

Example 249: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

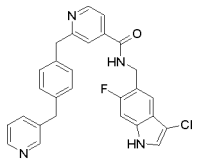


N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (30 mg, 21.5%) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 500.8, found 500.8. ^1H

NMR (DMSO-d_6, 300 MHz) δ 9.36-9.39 (m, 1 H), 8.63 (d, 1 H), 8.13-8.23 (m, 3 H), 7.54-7.77 (m, 4 H), 7.27-7.41 (m, 5 H), 6.85-6.87 (m, 1 H), 6.75 (d, 1 H), 6.42-6.45 (m, 1 H), 5.12 (d, 2 H), 4.60 (t, 1 H), 4.14 (d, 2 H).

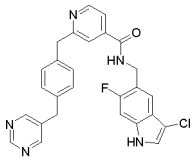
Example 250: Preparation of methyl N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyridin-3-ylmethyl)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyridin-3-ylmethyl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyridin-3-ylmethyl)benzyl)isonicotinamide (17 mg, 16%) was prepared as described for 2-(3-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 485.1, found 485.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.41 (s, 1 H), 9.25-9.22 (t, 1 H), 8.63-8.61 (d, 1 H), 8.49 (s, 1 H), 8.40-8.39 (d, 1 H), 7.70-7.45 (m, 5 H), 7.30-7.16 (m, 6 H), 4.60-4.59 (d, 1 H), 4.10 (s, 2 H), 3.92 (s, 2 H).

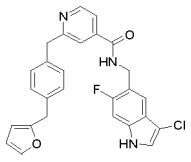
Example 251: Preparation of methyl N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyrimidin-5-ylmethyl)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-(4-(pyrimidin-5-ylmethyl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyrimidin-5-ylmethyl)benzyl)isonicotinamide (12 mg, 11%) was prepared as described for 2-(3-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 485.1, found 485.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.41 (s, 1 H), 9.24-9.22 (t, 1 H), 9.03 (s, 1 H), 8.70-8.60 (m, 3 H), 7.70 (s, 1 H), 7.64-7.62 (m, 1 H), 7.52-7.45 (m, 2 H), 7.25-7.19 (m, 5 H), 4.60-4.58 (d, 2 H), 4.11 (s, 2 H), 3.94 (s, 2 H).

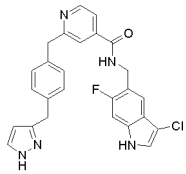
Example 252: Preparation of methyl N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(furan-2-ylmethyl)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(furan-2-ylmethyl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(furan-2-ylmethyl)benzyl)isonicotinamide (11 mg, 11%) was prepared as described for 2-(3-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 474.1, found 474.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.41 (s, 1 H), 9.24 (t, 1 H), 8.63-8.62 (d, 1 H), 7.70 (s, 1 H), 7.64-7.62 (d, 1 H), 7.52-7.44 (m, 3 H), 7.25-7.21 (m, 3 H), 7.15-7.13 (m, 2 H), 6.34 (s, 1 H), 6.11-6.10 (d, 1 H), 4.60-4.58 (d, 2 H), 4.11 (s, 2 H), 3.91 (s, 2 H).

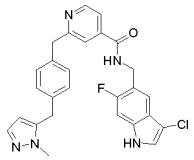
Example 253: Preparation of methyl 2-(4-((1H-pyrazol-3-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-(4-((1H-pyrazol-3-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

2-(4-((1H-pyrazol-3-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (13 mg, 13%) was prepared as described for 2-(3-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 474.1, found 474.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.44 (s, 1 H), 9.25 (t, 1 H), 8.63-8.61 (d, 1 H), 7.70-7.63 (m, 2 H), 7.51-7.44 (m, 3 H), 7.25-7.14 (m, 5 H), 7.06 (s, 1 H), 5.99 (s, 1 H), 4.59-4.58 (d, 2 H), 4.10 (s, 2 H), 3.87 (s, 2 H).

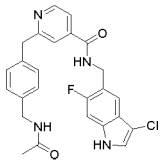
Example 254: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((1-methyl-1H-pyrazol-5-yl)methyl)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-(4-((1-methyl-1*H*-pyrazol-5-yl)methyl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((1-methyl-1H-pyrazol-5-yl)methyl)benzyl)isonicotinamide (10 mg, 9%) was prepared as described for 2-(3-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester as an off-white solid. LRMS ($M+H^+$) m/z calculated 488.2, found 488.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.53 (d, 1 H), 7.62 (s, 1 H), 7.59 (d, 1 H), 7.46 (d, 1 H), 7.28 (d, 1 H), 7.18-7.16 (m, 3 H), 7.09-7.05 (m, 3 H), 5.97 (d, 1 H), 4.64 (s, 2 H), 4.12 (s, 2 H), 4.95 (s, 2 H), 3.61 (s, 3 H).

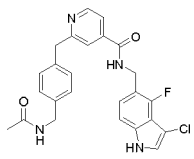
Example 255: Preparation of 2-(4-(acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-(4-(acetamidomethyl)benzyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)isonicotinamide

2-(4-(Acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (45 mg, 29% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 466.1, found 466.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.59 (d, 1 H), 7.68 (s, 1 H), 7.63 (dd, 1 H), 7.52 (d, 1 H), 7.27-7.22 (m, 5 H), 7.15 (d, 1 H), 4.71 (s, 2 H), 4.32 (s, 2 H), 4.20 (s, 2 H), 1.98 (s, 3 H).

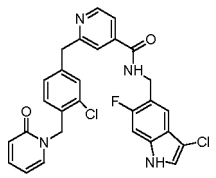
Example 256: Preparation of 2-(4-(acetamidomethyl)benzyl)-N-((3-chloro-4-fluoro-1H-indol-5-yl) methyl)isonicotinamide



2-(4-(acetamidomethyl)benzyl)-*N*-((3-chloro-4-fluoro-1*H*-indol-5-yl) methyl)isonicotinamide

2-(4-(Acetamidomethyl)benzyl)-N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)isonicotinamide (30 mg, 20%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 465, found 465. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.57 (br, 1 H), 9.19 (t, 1 H), 8.60 (d, 1 H), 8.24 (br, 1 H), 7.66 (s, 1 H), 7.60 (d, 1 H), 7.50 (d, 1 H), 7.10-7.23 (m, 6 H), 4.56 (s, 2 H), 4.18 (d, 2 H), 4.10 (s, 2 H), 1.83 (s, 3 H).

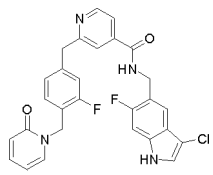
Example 257: Preparation of 2-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro- 6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

2-(3-Chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (15 mg, 12%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(6-pyrazol-1-ylmethyl-pyridin-3-ylmethyl)-isonicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 535, found 535. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.62 (d, 1 H), 7.77 (s, 1 H), 7.73 (d, 1 H), 7.50-7.59 (m, 3 H), 7.40 (s, 1 H), 7.23 (s, 1 H), 7.19 (d, 1 H), 7.12 (d, 1 H), 7.01 (d, 1 H), 6.56 (d, 1 H), 6.38 (t, 1 H), 5.24 (s, 2 H), 4.69 (d, 2 H), 4.21 (s, 2 H).

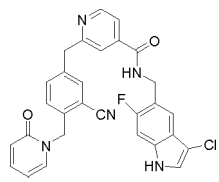
Example 258: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-fluoro-4-((2-oxopyridin -1(2H)-yl)methyl)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (83 mg, 59%) was prepared as described for 2-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 519, found 519. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.22 (t, 1 H), 8.63 (d, 1 H), 7.74 (d, 1 H), 7.69 (d, 1 H), 7.65 (d, 1 H), 7.50 (d, 1 H), 7.40-7.46 (m, 2 H), 7.22 (d, 1 H), 7.15 (d, 1 H), 7.04-7.10 (m, 2 H), 6.38 (d, 1 H), 6.23 (t, 1 H), 5.07 (s, 2 H), 4.58 (d, 2 H), 4.15 (s, 2 H).

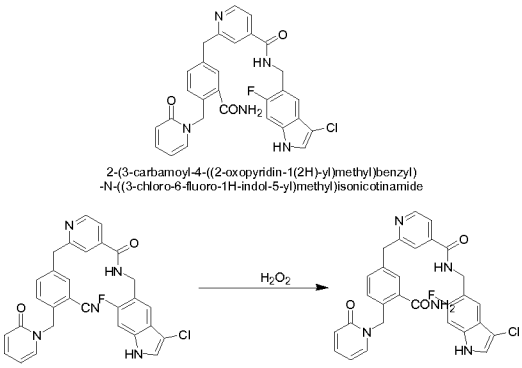
Example 259: Preparation of N-(3-Chloro-6-fluoro-1H-indol-5-ylmethyl)-2-[3-cyano-4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinamide



N-(3-Chloro-6-fluoro-1*H*-indol-5-ylmethyl)-2-[3-cyano-4-(2-oxo-2*H*-pyridin-1-ylmethyl)-benzyl]-isonicotinamide

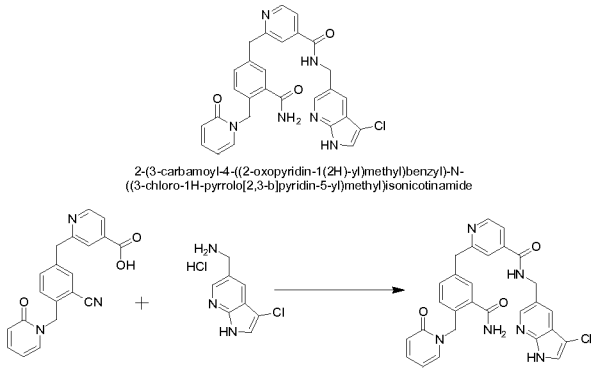
N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-[3-cyano-4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinamide (0.17 mg, 25.8%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS (M+H+) m/z calculated 526.1, found 526.1. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.37(d, 1 H), 9.21 (s, 1 H), 8.62-8.63 (d, 1 H), 7.45-7.49 (m, 8 H), 7.20 (d, 1 H), 7.03(d, 1 H), 6.39-6.42 (m, 1 H), 6.26-6.30 (m, 1 H), 5.22 (s, 2 H), 4.57-4.59 (d, 2 H), 4.19 (s, 2 H).

Example 260: Preparation of 2-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol- 5-yl)methyl)isonicotinamide



To a solution of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-cyano-4-((2-oxopyridin-1(2H)-yl) methyl)benzyl)isonicotinamide (60 mg) in DMF (2 mL) was added NH_3OH (2 mL) followed by 30% of H_2O_2 (0.2 mL). The resultant mixture was stirred for overnight. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give 2-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (10 mg, 16%) as a yellow solid. LRMS (M+H$^+$) m/z calculated 544, found 544. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.95 (s, 1 H), 8.85 (t, 1 H), 8.54 (d, 1 H), 8.40 (t, 1 H), 8.29 (d, 1 H), 7.86-7.92 (m, 2 H), 7.67-7.70 (m, 2 H), 7.24 (d, 1 H), 6.44 (d, 1 H), 5.15 (s, 2 H), 4.54 (d, 2 H), 4.29 (d, 2 H), 1.86 (s, 3 H).

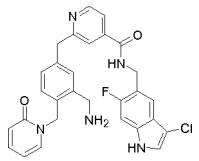
Example 261: Preparation of 2-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro -1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)isonicotinamide



To a solution of 2-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinic acid (150 mg, crude) in DMF (2 mL) was added (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl) methanamine hydrochloride (61 mg, 0.28 mmol, 1.0 eq) followed by EDCI (65 mg, 0.34 mmol, 1.2 eq), HOBT (46 mg, 0.34 mmol, 1.2 eq) and TEA (85 mg, 0.84 mmol, 3.0 eq). The reaction mixture was stirred for overnight. LCMS showed the SM was

consumed. To the mixture was added 85% of NH_4OH (1 mL) followed by 30% of H_2O_2.The mixture was stirred for 3 h and then concentrated. The residue was purified by prep-HPLC to give2-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl) benzyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)isonicotinamide (28 mg, 19%) as a white solid. LRMS ($M+H^+$) m/z calculated 527, found 527. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.94 (s, 1 H), 9.28 (t, 1 H), 8.61 (d, 1 H), 8.30 (s, 1 H), 8.05 (s, 1 H), 7.87 (s, 1 H), 7.71-7.73 (m, 2 H), 7.67 (s, 1 H), 7.61 (d, 2 H), 7.50 (s, 1 H), 7.41-7.45 (m, 2 H), 7.29 (d, 1 H), 6.88 (d, 1 H), 6.40 (d, 1 H), 6.23 (t, 1 H), 5.21 (s, 2 H), 4.58 (d, 2 H), 4.13 (s, 2 H).

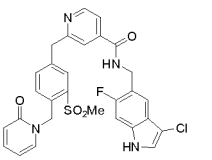
Example 262: Preparation of 2-(3-(aminomethyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3- chloro-6-fluoro-1H- indol-5-yl)methyl)isonicotinamide.



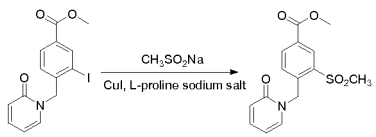
2-(3-(aminomethyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

2-(3-(Aminomethyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3- chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (20 mg, 10%) was prepared as described for 2-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro- 1H-indol-5-yl)methyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 529, found 529. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.38 (s, 1 H), 9.21 (t, 1 H), 8.61 (d, 1 H), 7.69 (s, 1 H), 7.61-7.64 (m, 2 H), 7.50 (s, 1 H), 7.41-7.45 (m, 2 H), 7.34 (s, 1 H), 7.22 (d, 1 H), 7.08 (d, 1 H), 6.76 (d, 1 H), 6.41 (d, 1 H), 6.22 (t, 1 H), 5.12 (s, 2 H), 4.57 (d, 2 H), 4.10 (s, 2 H), 3.75 (s, 2 H).

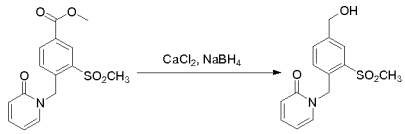
Example 263: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



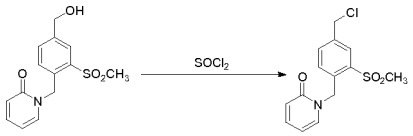
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide TFA salt



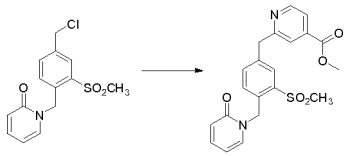
To a solution of 3-iodo-4-(2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester (2.0 g, 5.42 mmol, 1 eq) in DMSO (10 mL) was added *L*-proline sodium salt (160 mg , 1.08 mmol, 0.2 eq), CuI (103 mg, 0.54 mmol, 0.1 eq) and CH_3SO_2Na (663 mg, 6.50 mmol, 1.2 eq). The mixture was stirred at 110 ºC for 24 h. After cooling to rt the mixture was poured into water and the mixture was extracted with EA. The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (DCM/MeOH = 100/1, v/v) to give 3-methanesulfonyl-4-(2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester (460 mg, 26%) as an off white solid.



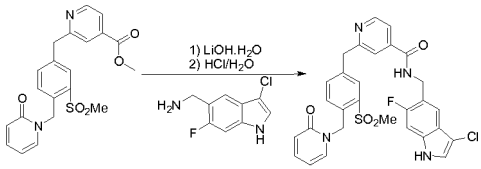
To a solution of 3-methanesulfonyl-4-(2-oxo-2H-pyridin-1-ylmethyl)-benzoic acid methyl ester (450 mg, 1.4 mmol, 1 eq) and $CaCl_2$ (154 mg, 1.4 mmol, 1 eq) in MeOH (15 mL) was added $NaBH_4$ (106 mg, 2.8 mmol, 2 eq) portionwise. The mixture was stirred at rt for 2 h and quenched by the addition of water. MeOH was removed by evaporation and the aqueous phase was extracted with EA. The combined extracts were dried and concentrated to give 1-(4-hydroxymethyl-2-methanesulfonyl-benzyl)-1H-pyridin-2-one (390 mg, 95%) as a white solid.



The mixture of 1-(4-hydroxymethyl-2-methanesulfonyl-benzyl)-1H-pyridin- 2-one (390 mg, 1.33 mmol, 1 eq) and $SOCl_2$ (5 mL) was stirred at rt for 1 h. The volatiles were then removed at 40 °C in *vacuum* and the residue was dissolved in DCM. The mixture was washed with saturated aq. $NaHCO_3$, dried and concentrated to give 1-(4-chloromethyl-2-methanesulfonyl-benzyl)-1H-pyridin-2-one (390 mg, 94%) as a white solid.

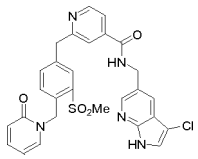


2-[3-Methanesulfonyl-4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-isonicotinic acid methyl ester (320 mg, 62%) was prepared as described for 2-[6-(2-oxo-2*H*-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]-isonicotinic acid methyl ester as a yellow solid.



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (10 mg, 14% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin- 2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 485.1, found 485.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.39 (d, 1 H), 9.23 (t, 1 H), 8.63-8.62 (d, 1 H), 7.91-7.77 (m, 3 H), 7.65-7.44 (m, 5 H), 7.24-7.21 (d, 1 H), 6.85-6.82 (d, 1 H), 6.65-6.34 (m, 2 H), 5.43 (s, 2 H), 4.59-4.58 (d, 2 H), 4.24 (s, 2 H), 2.50 (d, 3 H).

Example 264: Preparation of N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

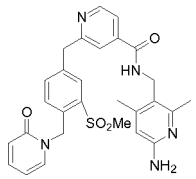


N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (30 mg, 44% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin- 2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 562.1, found 562.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.96 (s, 1 H),

9.33 (t, 1 H), 8.65-8.63 (d, 1 H), 8.30 (d, 1 H), 7.91-7.78 (m, 4 H), 7.68-7.64 (m, 2 H), 7.59-7.50 (m, 2 H), 6.85-6.82 (d, 2 H), 6.45-6.32 (m, 2 H), 5.43 (s, 2 H), 4.60-4.58 (d, 2 H), 4.25 (d, 2 H).

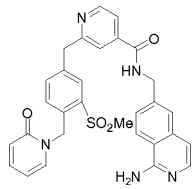
Example 265: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (18 mg, 28% yield for 2 steps) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl) methyl)isonicotinamide as an off-white solid. LRMS ($M+H^+$) m/z calculated 532.1, found 532.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.63-8.57 (m, 2 H), 7.90-7.85 (m, 2 H), 7.72 (s, 1 H), 7.60-7.50 (m, 3 H), 6.85-6.83 (d, 1 H), 6.45-6.33 (m, 2 H), 6.13 (s, 1 H), 5.68 (s, 2 H), 4.35-4.34 (d, 2 H), 4.23 (s, 2 H), 3.40-3.38 (m, 3 H), 2.30 (s, 3 H), 2.16 (s, 3 H).

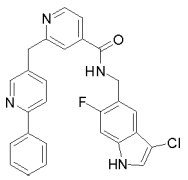
Example 266: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide



N-((1-aminoisoquinolin-6-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide (9 mg, 28% yield for 2 steps) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl) isonicotinamide as an off-white solid. LRMS ($M+H^+$) m/z calculated 554.1, found 554.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.39 (t, 1 H), 8.65-8.64 (d, 1 H), 8.15-8.13 (d, 1 H), 7.92-7.89 (m, 2 H), 7.87-7.79 (m, 2 H), 7.77-7.75 (d, 1 H), 7.68-7.52 (m, 3 H), 7.41-7.39 (dd, 1 H), 6.87-6.83 (m, 2 H), 6.72 (s, 2 H), 6.45-6.42 (d, 1 H), 6.34 (t, 1 H), 5.43 (s, 2 H), 4.62-4.60 (d, 2 H), 4.26 (s, 2 H), 3.40 (s, 3 H).

Example 267: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-phenylpyridin-3-yl)methyl)isonicotinamide

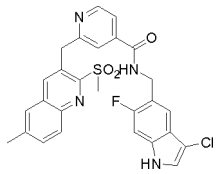


N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-phenylpyridin-3-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-phenylpyridin-3-yl)methyl)isonicotinamide (34 mg, 24% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a yellow solid. LRMS ($M+H^+$) m/z calculated 471.1, found 471.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.39 (s, 1 H), 9.25 (t, 1 H), 8.66-8.63 (m, 2 H), 8.06-8.02 (dd,

2 H), 7.89-7.87 (d, 1 H), 7.80-7.75 (m, 2 H), 7.67-7.65 (m, 1 H), 7.50-7.40 (m, 5 H), 7.25-7.21 (d, 1 H), 4.61-4.59 (d, 2 H), 3.85 (s, 2 H).

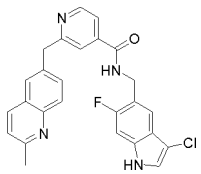
Example 268: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-methyl-2-(methylsulfonyl)quinolin-3-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-methyl-2-(methylsulfonyl)quinolin-3-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-methyl-2-(methylsulfonyl)quinolin-3-yl)methyl)isonicotinamide (19 mg, 13% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-yl methyl]-nicotinamide as purple solid. LRMS ($M+H^+$) m/z calculated 537.1, found 537.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.40 (s, 1 H), 9.27-9.24 (t, 1 H), 8.63-8.62 (d, 1 H), 8.31 (s, 1 H), 8.02-8.00 (d, 1 H), 7.82 (s, 1 H), 7.75-7.45 (m, 5 H), 7.24-7.21 (d, 1 H), 4.78 (s, 2 H), 4.60-4.58 (d, 2 H), 3.52 (s, 3 H), 2.52-2.51 (t, 3 H).

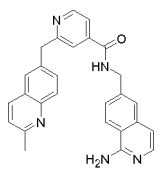
Example 269: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide (16 mg, 15% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a yellow solid. LRMS ($M+H^+$) m/z calculated 459.1, found 459.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.39 (s, 1 H), 9.24 (t, 1 H), 8.66-8.64 (d, 1 H), 8.18-8.16 (d, 1 H), 7.85-7.78 (m, 3 H), 7.65-7.62 (m, 2 H), 7.50-7.36 (m, 3 H), 7.24-7.20 (d, 1 H), 4.59-4.57 (d, 2 H), 4.33 (s, 2 H), 2.62 (s, 3 H).

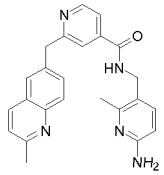
Example 270: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide



N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide (30 mg, 20% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 434.2, found 434.2. ^1H NMR (CD_3OD, 300 MHz) δ 8.64 (d, 1 H), 8.14 (d, 1 H), 8.06 (d, 1 H), 7.88 (d, 1 H), 7.77-7.59 (m, 6 H), 7.47 (d, 1 H), 7.37 (d, 1 H), 6.90 (d, 1 H), 4.69 (s, 2 H), 4.38 (s, 2 H) , 2.68 (s, 3 H).

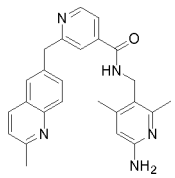
Example 271: Preparation of N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide



N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide

N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide (29 mg, 14% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide as a yellow solid. LRMS ($M+H^+$) m/z calculated 398.1, found 398.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.02 (t, 1 H), 8.65-8.63 (d, 1 H), 8.18-8.16 (d, 1 H), 7.86-7.63 (m, 5 H), 7.38-7.36 (d, 2 H), 7.26-7.24 (d, 1 H), 6.25-6.23 (d, 1 H), 5.77-5.76 (d, 2 H), 4.33-4.29 (m, 4 H), 2.63 (s, 3 H), 2.23 (s, 3 H).

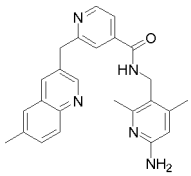
Example 272: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide (45 mg, 16%) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 411.9, found 411.9. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.59-8.65 (m, 2 H), 8.17 (d, 1 H), 7.83 (d, 1 H), 7.75 (d, 2 H), 7.58-7.64 (m, 2 H), 7.37 (d, 1 H), 6.11 (s, 1 H), 5.67 (s, 2 H), 4.30-4.34 (m, 3 H), 2.61 (d, 3 H), 2.29 (s, 3 H), 2.15 (s, 3 H).

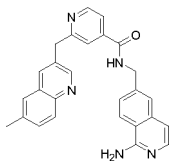
Example 273: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide (29 mg, 21% yield for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide as a yellow solid. LRMS ($M+H^+$) m/z calculated 412.1, found 412.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.72 (s, 1 H), 8.57-8.52 (d, 2 H), 8.00 (s, 1 H), 7.80-7.58 (m, 2 H), 7.53-7.44 (m, 3 H), 6.05 (s, 1 H), 5.62 (s, 2 H), 4.26 (s, 4 H), 2.42-2.39 (m, 3 H), 2.22 (s, 3 H), 2.07 (s, 3 H).

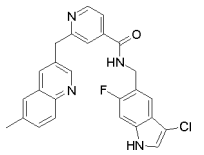
Example 274: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide



N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide (27 mg, 18% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 434.2, found 434.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.74 (d, 1 H), 8.66 (d, 1 H), 8.11 (s, 1 H), 8.07 (d, 1 H), 7.88 (d, 1 H), 7.83 (s, 1 H), 7.72 (d, 1 H), 7.69 (d, 1 H), 7.61 (s, 2 H), 7.51 (d, 1 H), 7.49 (d, 1 H), 6.92 (d, 1 H), 4.71 (s, 2 H), 4.41 (s, 2 H) , 2.51 (s, 3 H).

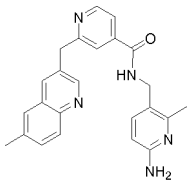
Example 275: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-methylquinolin-3-yl)methyl) isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-((6-methylquinolin-3-yl) methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-methyl quinolin-3- yl) methyl)isonicotinamide (62 mg, 40%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as an off-white solid. LRMS ($M+H^+$) m/z calculated 459, found 459. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.24 (t, 1 H), 8.80 (s, 1 H), 8.64 (d, 1 H), 8.09 (s, 1 H), 7.87 (d, 1 H), 7.81 (s, 1 H), 7.65-7.67 (m, 2 H), 7.50-7.55 (m, 2 H), 7.45 (d, 1 H), 7.23 (d, 1 H), 4.59 (d, 2 H), 4.37 (s, 2 H), 2.48 (s, 3 H).

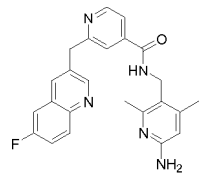
Example 276: Preparation of N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide



N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide (30 mg, 20% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 438.2, found 438.2. ^1H NMR (CD_3OD, 300 MHz) δ 8.81 (d, 1 H), 8.66 (d, 1 H), 8.20 (d, 1 H), 8.08 (d, 1 H), 8.05 (dd, 1 H), 7.83 (s, 1 H), 7.71 (d, 1 H), 7.70 (d, 1 H), 7.62 (s, 1 H), 7.57-7.47 (m, 3 H), 6.93 (d, 1 H), 4.72 (s, 2 H), 4.44 (s, 2 H).

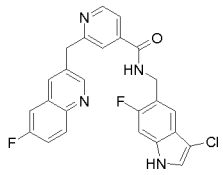
Example 278: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide (35 mg, 25% yield for 2 steps) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide as an off-white solid. LRMS ($M+H^+$) m/z calculated 416.1, found 416.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.87-8.86 (d, 1 H), 8.66-8.58 (m, 2 H), 8.18 (d, 1 H), 8.06-8.02 (m, 1 H), 7.78-7.72 (m, 2 H), 7.64-7.58 (m, 2 H), 6.11 (s, 2 H), 5.68 (s, 2 H), 4.36-4.33 (m, 4 H), 2.30 (s, 3 H), 2.16 (s, 3 H).

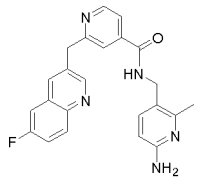
Example 279: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide (42 mg, 26.8%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 463.1, found 463.1. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.41 (s, 1 H), 9.26 (t, 1 H), 8.88 (d, 1 H), 8.65 (d, 1 H), 8.10 (s, 1 H), 8.02-8.07 (m, 1 H), 7.82 (s, 1 H), 7.74 (dd, 1 H), 7.61-7.67 (m, 2 H), 7.51 (s, 1 H), 7.45 (d, 1 H), 7.22 (d, 1 H), 4.59 (d, 2 H), 4.39 (s, 2 H).

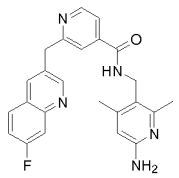
Example 280: Preparation of N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide



N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide

N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide (18 mg, 13.2%) was prepared as described for N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 401.9, found 401.9. ^1H NMR (CD_3OD, 300 MHz) δ 8.80 (d, 1 H), 8.63 (d, 1 H), 8.20 (s, 1 H), 8.01-8.04 (m, 1 H), 7.78 (s, 1 H), 7.63-7.64 (m, 1 H), 7.52-7.58 (m, 3 H), 7.40 (d, 1 H), 4.43 (d, 4 H), 2.38 (s, 3 H).

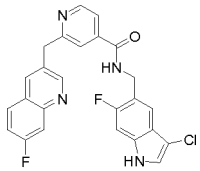
Example 281: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide (35 mg, 25%) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 415.9, found 415.9. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.92 (d, 1 H), 8.65 (t, 1 H), 8.60 (d, 1 H), 8.26 (s, 1 H), 8.04 (dd, 1 H), 7.79 (s, 1 H), 7.73 (dd, 1 H), 7.61 (d, 1 H), 7.51-7.55 (m, 1 H), 6.13 (s, 1 H), 5.68 (s, 2 H), 4.35-4.37 (m, 4 H), 2.31 (s, 3 H), 2.17 (s, 3 H).

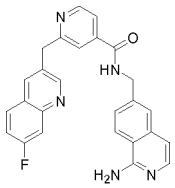
Example 282: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide (45 mg, 28.7%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 462.8, found 462.8. ^1H NMR (DMSO-d_6, 300 MHz) δ 11.39-11.42 (m, 1 H), 9.26 (t, 1 H), 8.92 (s, 1 H), 8.64 (d, 1 H), 8.27 (s, 1 H), 8.04 (dd, 1 H), 7.82 (s, 1 H), 7.65-7.74 (m, 2 H), 7.43-7.55 (m, 3 H), 7.22 (d, 1 H), 4.59 (d, 2 H), 4.38 (s, 2 H).

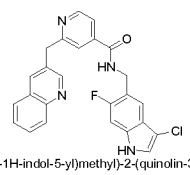
Example 283: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide



N-((1-aminoisoquinolin-6-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide (16 mg, 10.8%) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 437.8, found 437.8. ^1H NMR (CD_3OD, 400 MHz) δ 8.72 (d, 1 H), 8.52 (d, 1 H), 8.09 (s, 1 H), 7.93 (d, 1 H), 7.77-7.80 (m, 1 H), 7.70 (s, 1 H), 7.56-7.58 (m, 2 H), 7.47-7.50 (m, 2 H), 7.35 (d, 2 H), 7.26-7.31 (m, 1 H), 6.78 (d, 1 H), 4.58 (s, 2 H), 4.29 (s, 2 H).

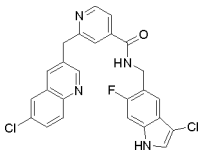
Example 284: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(quinolin-3-ylmethyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(quinolin-3-ylmethyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(quinolin-3-ylmethyl)isonicotinamide (24 mg, 17% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a yellow solid. LRMS ($M+H^+$) m/z calculated 445.1, found 445.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.40 (s, 1 H), 9.26 (t, 1 H), 9.01 (s, 1 H), 8.66-8.65 (d, 1 H), 8.40 (s, 1 H), 8.05-8.00 (t, 2 H), 7.85 (s, 1 H), 7.80 (t, 1 H), 7.69-7.66 (m, 2 H), 7.51-7.44 (m, 2 H), 7.24-7.21 (d, 1 H), 4.60-4.59 (d, 2 H), 4.44 (s, 2 H).

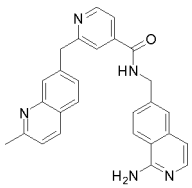
Example 285: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-chloroquinolin-3-yl) methyl)isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-((6-chloroquinolin-3-yl) methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-chloro quinolin-3-yl)methyl) isonicotinamide (12 mg, 15%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as an off-white solid. LRMS ($M+H^+$) m/z calculated 479, found 479. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.25 (t, 1 H), 8.92 (d, 1 H), 8.64 (d, 1 H), 8.20 (s, 1 H), 8.08 (d, 1 H), 8.00 (d, 1 H), 7.82 (s, 1 H), 7.71 (d, 1 H), 7.66 (d, 2 H), 7.50 (d, 2 H), 7.45 (d, 1 H), 7.22 (d, 1 H), 4.59 (d, 2 H), 4.40 (s, 2 H).

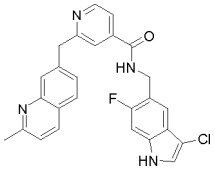
Example 286: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide



N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide (35 mg, 22%) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2- (4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 434, found 434.^1H NMR (DMSO-d_6, 400 MHz) δ 9.39 (t, 1 H), 8.67 (d, 1 H), 8.18 (d, 1 H), 8.13 (d, 1 H), 7.80-7.85 (m, 3 H),7.75 (d, 1 H), 7.68 (d, 1 H), 7.54 (s, 1 H), 7.47 (d, 1 H), 7.35- 7.40 (m, 2 H), 6.84 (d, 1 H), 6.72 (s, 2 H), 4.60 (d, 2 H), 4.37 (s, 2 H), 2.62 (s, 3 H).

Example 287: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide

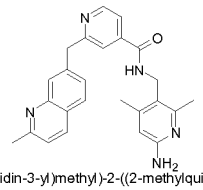


N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide (25 mg, 15%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-

pyridin-3-ylmethyl]-nicotinamide. LRMS (M+H+) m/z calculated 459, found 459. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.40 (br, 1 H), 9.26 (t, 1 H), 8.65 (d, 1 H), 8.17 (d, 1 H), 7.79-7.84 (m, 3 H),7.65 (d, 1 H), 7.42- 7.50 (m, 3 H), 7.35 (d, 1 H), 7.22 (d, 2 H), 4.57 (d, 2 H), 4.35 (s, 2 H), 2.62 (s, 3 H).

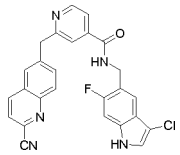
Example 288: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide (10 mg, 7%) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS (M+H$^+$) m/z calculated 412, found 412. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.59 - 8.64 (m, 2 H), 8.17 (d, 1 H), 7.82 (d, 1 H), 7.76 (d, 2 H), 7.60 (d, 1 H), 7.45 (d, 1 H), 7.35 (d, 1 H), 6.10 (s, 1 H), 5.67 (s, 2 H), 4.33 (s, 4 H), 2.62 (s, 3 H), 2.29 (s, 3 H), 2.15 (s, 3 H).

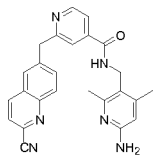
Example 289: Preparation of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(2-cyano-quinolin-6-ylmethyl)-isonicotinamide



N-(3-Chloro-6-fluoro-1*H*-indol-5-ylmethyl)-2-(2-cyano-quinolin-6-ylmethyl)-isonicotinamide

N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(2-cyano-quinolin-6-ylmethyl)-isonicotinamide (90 mg, 22% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS (M+H$^+$) m/z calculated 570.1, found 570.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.41 (s, 1 H), 9.26 (t, 1 H), 8.60-8.65 (m, 2 H), 8.00-8.08 (m, 3 H), 7.87-7.89 (dd, 1 H), 7.81 (s, 1 H), 7.66-7.67 (dd, 1 H), 7.50-7.51 (d, 1 H), 7.43-7.45 (d, 1 H), 7.21-7.24 (d, 1 H), 4.58-4.59 (d, 2 H), 4.42 (s, 2 H).

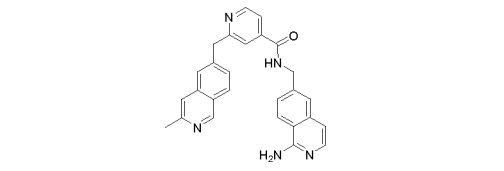
Example 290: Preparation of N-(6-amino-2,4-dimethyl-pyridin-3-ylmethyl)-2-(2-cyano-quinolin-6-ylmethyl)-isonicotinamide



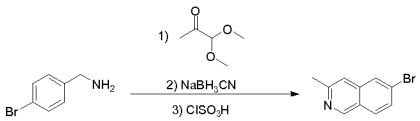
N-(6-Amino-2,4-dimethyl-pyridin-3-ylmethyl)-2-(2-cyano-quinolin-6-ylmethyl)-isonicotinamide

N-(6-amino-2,4-dimethyl-pyridin-3-ylmethyl)-2-(2-cyano-quinolin-6-ylmethyl)-isonicotinamide (90 mg, 26% yields for 2 steps) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS (M+H$^+$) m/z calculated 423.1, found 423.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.60-8.64 (m, 3 H), 8.00-8.07 (m, 3 H), 7.86-7.88 (m, 1 H), 7.78 (s, 1 H), 7.61-7.62 (d, 1 H), 6.12 (s, 1 H), 5.68 (s, 2 H), 4.33-4.40 (m, 4 H), 2.30 (s, 3 H), 2.16 (s, 3 H).

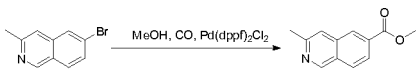
Example 291: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide



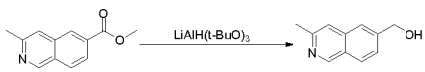
N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide



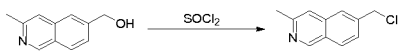
To a solution of 4-bromo-benzylamine (10. 0 g, 54 mmol, 1.0 eq) in DCE (100 mL) was added 1,1-dimethoxy-propan-2-one (7.0 g, 59 mmol, 1.1 eq) and $MgSO_4$ (20 g). The mixture was stirred at 40 °C overnight. Then to the mixture was added $NaBH_3CN$ (4.08 g, 64.8 mmol, 1.2 eq). After stirring at rt for 5 h the mixture was filtered. The filtrate was concentrated to give a yellow oil. Chlorosulfonic acid (30 mL) was cooled to -10 °C and the above crude product was added dropwise. The reaction mixture was heated to 100 °C for 10 min, then cooled and poured into ice. The mixture was neutralized with 2M NaOH and extracted with EA. The combined extracts were dried and concentrated. The residue was purified by silica gel chromatography (PE/EA = 2/1, v/v) to afford 6-bromo-3-methyl-isoquinoline (4.0 g, 34% yield for 3 steps) as a yellow solid.



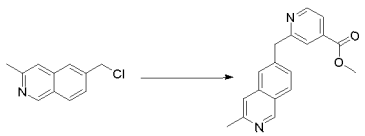
An autoclave vessel was charged with 6-bromo-3-methyl-isoquinoline (4.0 g, 18 mmol), $Pd(dppf)Cl_2$ (735 mg, 0.9 mmol, 0.05 eq) and triethylamine (5.0 mL, 36 mmol, 2 eq) in 40 mL of methanol. The vessel was purged with nitrogen three times and carbon monoxide three times. The vessel was pressurized to 3 MPa with carbon monoxide and heated to 100 °C. The reaction was thus stirred overnight, then allowed to cool to room temperature. The resulting solution was concentrated and purified by flash chromatography on silica gel (PE/EA = 1/1, v/v) to afford 3-methyl-isoquinoline-6-carboxylic acid methyl ester (3.4 g, 94%) as a white solid.



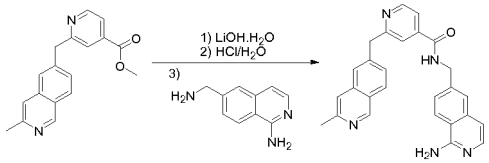
To a solution of 3-methyl-isoquinoline-6-carboxylic acid methyl ester (3.3 g, 16.42 mmol, 1 eq) in dry THF (100 mL) was added $LiAlH(t\text{-}BuO)_3$ (12.5 g, 45.25 mmol, 3 eq). The resulting mixture was stirred at 60 °C for 5 h and then quenched by the addition of water. The mixture was extracted with EA. The combined extracts were dried and concentrated. The residue was purified by silica gel chromatography (PE/EA = 1/1, v/v) to afford (3-methyl-isoquinolin-6-yl)-methanol (2.5 g, 89%) as a white solid.



To (3-methyl-isoquinolin-6-yl)-methanol (1.5 g, 8.67 mmol, 1 eq) was added $SOCl_2$ (9 mL) and the mixture was stirred at rt for 3 h. The volatiles were then removed at 40 °C under vacuum and the residue was dissolved in DCM. The mixture was washed with saturated aq. $NaHCO_3$, dried and concentrated to give 6-chloromethyl-3-methyl-isoquinoline (1.4 g, 85%) as a white solid.

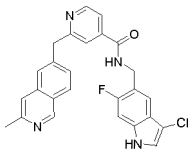


2-(3-Methyl-isoquinolin-6-ylmethyl)-isonicotinic acid methyl ester (1.0 g, 47%) was prepared as described for 2-[6-(2-oxo-2*H*-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]- isonicotinic acid methyl ester.



N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide (20 mg, 14% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS (M+H$^+$) m/z calculated 434.2, found 434.2. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.06 (s, 1 H), 8.66 (d, 1 H), 8.08 (d, 1 H), 7.97 (d, 1 H), 7.80 (s, 1 H), 7.71 (s, 2 H), 7.70 (s, 1 H), 7.62 (s, 1 H), 7.56 (s, 1 H), 7.50 (d, 1 H), 7.47 (d, 1 H), 6.92 (d, 1 H), 4.71 (s, 2 H), 4.11 (s, 2 H), 2.64 (s, 3 H).

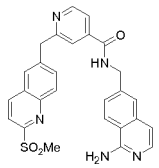
Example 292: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide (43 mg, 28% yields for 2 steps) was prepared as discrbed for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS (M+H$^+$) m/z calculated 459.1, found 459.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.42 (s, 1 H), 9.26 (t, 1 H), 9.15 (s, 1 H), 8.67 (d, 1 H), 8.00 (dd, 1 H), 7.79 (s, 1 H), 7.72 (s, 1 H), 7.67 (d, 1 H), 7.58 (s, 1 H), 7.53 (d, 1 H), 7.52 (s, 1 H), 7.46 (d, 1 H), 7.24 (d, 1 H), 4.60 (d, 2 H), 4.36 (s, 2 H), 2.59 (s, 3 H).

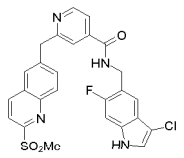
Example 293: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide



N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide

N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide (34 mg, 34% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS (M+H$^+$) m/z calculated 498.2, found 498.2. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.66 (d, 1 H), 8.49 (d, 1 H), 8.06 (d, 1 H), 8.03 (d, 1 H), 8.02 (s, 1 H), 7.88 (s, 1 H), 7.81 (s, 1 H), 7.78 (d, 1 H), 7.69 (d, 1 H), 7.67 (d, 1 H), 7.59 (s, 1 H), 7.46 (d, 1 H), 6.88 (d, 1 H), 4.69 (s, 2 H), 4.43 (s, 2 H), 3.37 (s, 3 H).

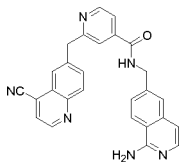
Example 294: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide



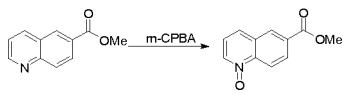
N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-((2-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide (24 mg, 23% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 523.1, found 523.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.53 (d, 1 H), 8.47 (d, 1 H), 8.02 (d, 1 H), 7.99 (d, 1 H), 7.84 (s, 1 H), 7.75 (d, 1 H), 7.68 (s, 1 H), 7.56 (d, 1 H), 7.40 (d, 1 H), 7.13(s, 1 H), 7.02 (s, 1 H), 4.58 (s, 2 H), 4.36 (s, 2 H), 3.25 (s, 3 H).

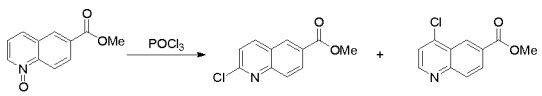
Example 295: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide



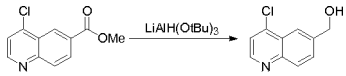
N-((1-aminoisoquinolin-6-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide



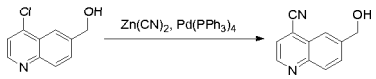
A mixture of quinoline-6-carboxylic acid methyl ester (10 g, 53.5 mmol, 1 eq) and m-CPBA (18.4 g, 0.106 mol, 2 eq) in DCM (50 mL) was stirred at rt overnight. Saturated aq. $NaHCO_3$ (40 mL) was added to the reaction mixture and it was stirred for 30 min. The organic layer was separated, dried, filtered and concentrated to obtain a residue, which was re-crystallized by EA (5 mL) to afford 1-oxy-quinoline-6-carboxylic acid methyl ester (8.0 g, 74%) as a light yellow solid.



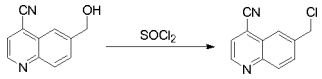
To 1-oxy-quinoline-6-carboxylic acid methyl ester (4.0 g, 19.7 mmol, 1 eq) was added phosphoryl trichloride (20 mL). The resulting mixture was then stirred at rt under N_2 for 2 h. The volatiles were then removed under vacuum and the residue was dissolved in DCM. The mixture was washed with saturated aq. $NaHCO_3$, dried and concentrated. The residue was purified by silica gel chromatography (PE/EA = 10/1, v/v) to afford 2-chloro-quinoline-6-carboxylic acid methyl ester (1.2 g, 28%) and 4-chloro-quinoline-6-carboxylic acid methyl ester (2.5 g, 57%).



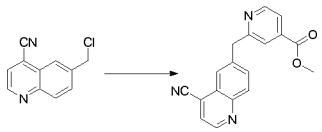
To a solution of 4-chloro-quinoline-6-carboxylic acid methyl ester (2.2 g, 10 mmol, 1 eq) was added $LiAlH(t\text{-}BuO)_3$ (7.62 g, 30 mmol, 3 eq). The resulting mixture was stirred at 60 °C for 2 h and then quenched by the addition of water. The mixture was extracted with EA. The combined extracts were dried and concentrated. The residue was purified by silica gel chromatography (PE/EA = 1/1, v/v) to afford (4-chloro-quinolin-6-yl)-methanol (1.54 g, 80%) as a yellow solid.



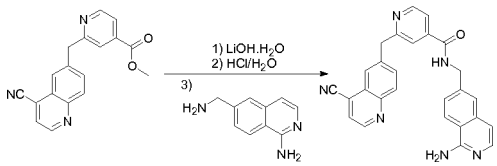
6-Hydroxymethyl-quinoline-4-carbonitrile (1.1 g, 77%) was prepared as described for as 1-(4-hydroxymethyl-2-methanesulfonyl-benzyl)-1H-pyridin-2-one as an off-white solid.



6-Chloromethyl-quinoline-4-carbonitrile (1.0 g, 83%) was prepared as described for as 1-(4-chloromethyl-2-methanesulfonyl-benzyl)-1H-pyridin-2-one as a white solid.

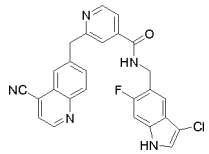


2-(4-Cyano-quinolin-6-ylmethyl)-isonicotinic acid methyl ester (1.0 g, 67%) was prepared as described for 2-[6-(2-oxo-2*H*-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]- isonicotinic acid methyl ester as a yellow solid.



N-((1-aminoisoquinolin-6-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide (43 mg, 29% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 445.2, found 445.2. ^1H NMR (CD_3OD, 300 MHz) δ 9.40 (t, 1 H), 9.06 (d, 1 H), 8.69 (d, 1 H), 8.15-8.11 (m, 3 H), 8.06 (s, 1 H), 7.92 (d, 1 H), 7.87 (s, 1 H), 7.77 (d, 1 H), 7.71 (d, 1 H), 7.56 (s, 1 H), 7.41 (d, 1 H), 6.85 (d, 1 H), 6.73 (s, 2 H), 4.62 (d, 2 H) , 4.50 (s, 2 H).

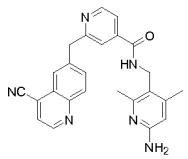
Example 296: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide (45 mg, 29% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a yellow solid. LRMS ($M+H^+$) m/z calculated 470.1, found 470.1. ^1H NMR (DMSO, 400 MHz) δ 11.42 (s, 1 H), 9.28 (t, 1 H), 9.07 (d, 1 H), 8.68 (d, 1 H), 8.14 (d, 1 H), 8.12 (s, 1 H), 8.06 (s, 1 H), 7.91 (d, 1 H), 7.86 (s, 1 H), 7.68 (d, 1 H), 7.51 (d, 1 H), 7.46 (d, 1 H), 7.24 (d, 1 H), 4.60 (d, 1 H), 4.49 (s, 2 H).

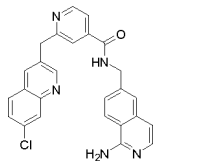
Example 297: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide



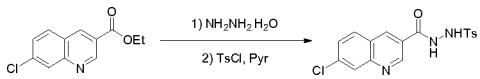
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide (23 mg, 17% yields for 2 steps) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide as a yellow solid. LRMS ($M+H^+$) m/z calculated 423.2, found 423.2. ^1H NMR (CD_3OD, 300 MHz) δ 8.98 (d, 1 H), 8.63 (d, 1 H), 8.10 (d, 1 H), 8.07 (s, 1 H), 7.93 (d, 1 H), 7.86 (dd, 1 H), 7.77 (s, 1 H), 7.63 (dd, 1 H), 6.29 (s, 1H), 4.50 (s, 2 H), 4.49 (s, 2 H), 2.38 (s, 3 H), 2.26 (s, 3 H).

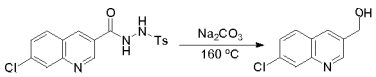
Example 298: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide



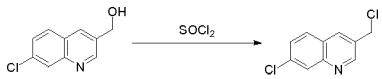
N-((1-aminoisoquinolin-6-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide



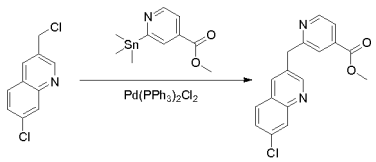
To a solution of 7-chloro-quinoline-3-carboxylic acid ethyl ester (3.5 g, 14.90 mmol, 1.0 eq) in EtOH (60 mL) was added hydrazine monohydrate (7.2 mL, 149 mmol, 10 eq). The reaction mixture was stirred at 80 °C for 2 h, and then concentrated under reduced pressure. Water was added to the reaction flask and the solid was filtered and washed with cold water. The solid was dried in air and then dissolved in pyridine (30 mL). To the mixture was added TsCl (3.4 g, 17.90 mmol, 1.2 eq). After stirring at rt for 1 h, the mixture was concentrated in vacuo. The residue was poured into water and the resulting precipitate was collected by filtration to give N-(7-chloro-quinoline-3-carbonyl)-N'-(toluene-4-sulfonyl)- hydrazine (5.0 g, 90%) as a yellow solid.



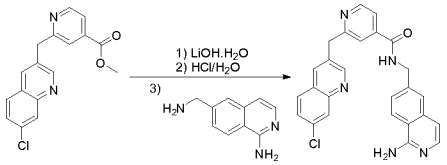
A mixture of 7 N-(7-chloro-quinoline-3-carbonyl)-N'-(toluene-4-sulfonyl)- hydrazine (5.0 g, 13.30 mmol, 1.0 eq) and Na_2CO_3 (4.24 g, 40 mmol, 3 eq) in ethylene glycol (30 mL) was heated at 160 °C for 20 min. After cooling to rt the mixture was diluted with water and extracted with Et_2O. The combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (PE/EA = 1/1, v/v) to give (7-chloro-quinolin-3-yl)-methanol (600 mg, 23%) as a yellow solid.



7-Chloro-3-chloromethyl-quinoline (550 mg, 84%) was prepared as described for as 1-(4-chloromethyl-2-methanesulfonyl-benzyl)-1H-pyridin-2-one as a yellow solid.

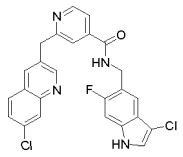


2-(7-Chloro-quinolin-3-ylmethyl)-isonicotinic acid methyl ester (400 mg, 49%) was prepared as described for 2-[6-(2-oxo-2*H*-pyridin-1-ylmethyl)-pyridin-3-ylmethyl]- isonicotinic acid methyl ester as a yellow solid.



N-((1-aminoisoquinolin-6-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide (34 mg, 23% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide. LRMS (M+H$^+$) m/z calculated 454.1, found 454.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.42 (d, 1 H), 8.96 (s, 1 H), 8.68 (d, 1 H), 8.20 (s, 1 H), 8.15 (d, 1 H), 8.05 (s, 1 H), 8.02 (d, 1 H), 7.86 (s, 1 H), 7.78 (d, 1 H), 7.70 (d, 1 H), 7.63 (dd, 1 H), 7.56 (s, 1 H), 7.42 (d, 1 H), 6.86 (d, 1 H), 4.63 (d, 2 H), 4.42 (s, 2 H).

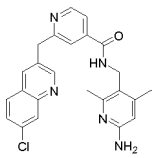
Example 299: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide (35 mg, 23% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS (M+H$^+$) m/z calculated 479.1, found 479.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.42 (s, 1H), 9.27 (t, 1 H), 8.95 (d, 1 H), 8.66 (d, 1 H), 8.27 (s, 1 H), 8.04 (d, 1 H), 8.01 (d, 1 H), 7.83 (s, 1 H), 7.67 (d, 1 H), 7.62 (dd, 1 H), 7.52 (d, 1 H), 7.46 (d, 1 H), 7.25 (d, 1 H), 4.60 (d, 2 H), 4.40 (s, 2 H).

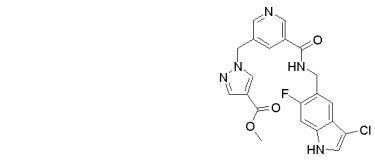
Example 300: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide



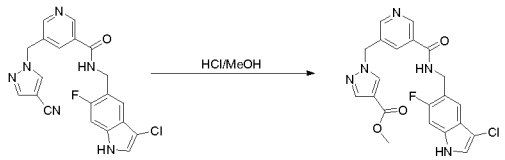
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide (10 mg, 7% yields for 2 steps) was prepared as described for N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide as a white solid. LRMS (M+H$^+$) m/z calculated 432.2, found 432.2. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.87 (d, 1 H), 8.63 (d, 1 H), 8.25 (s, 1 H), 8.00 (s, 1 H), 7.91 (d, 1 H), 7.78 (s, 1 H), 7.63 (d, 1 H), 7.60 (dd, 1 H), 6.32 (s, 1 H), 4.53 (d, 2 H), 4.44 (s, 2 H), 2.41 (s, 3 H), 2.29 (s, 3 H).

Example 301: Preparation of methyl 1-((5-(((3-chloro-6-fluoro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxylate

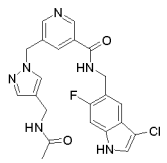


methyl 1-((5-(((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-1*H*-pyrazole-4-carboxylate



To a solution of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((4-cyano-1H- pyrazol-1-yl)methyl)nicotinamide (100 mg, 0.25 mmol, 1 eq) in MeOH (1 mL) was added HCl/MeOH solution. The mixture was stirred at rt for 5 h and concentrated in vacuo. The residue was purified by prep-HPLC to give methyl 1-((5-(((3-chloro-6-fluoro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxylate (9.1 mg, 8%) as a white solid. LRMS ($M+H^+$) m/z calculated 442.1, found 442.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.96 (d, 1 H), 8.63 (d, 1 H), 8.20 (s, 1 H), 8.16 (t, 1 H), 7.93 (s, 1 H), 7.54 (d, 1 H), 7.25 (s, 1 H), 7.15 (d, 1 H), 5.48 (s, 2 H), 4.72 (s, 2 H), 3.82 (s, 3 H).

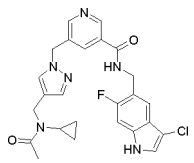
Example 302: Preparation of 5-((4-(acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide



5-((4-(acetamidomethyl)-1*H*-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)nicotinamide

5-((4-(Acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide (63 mg, 44% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 455.1, found 455.1. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.81 (d, 1 H) 8.44 (d, 1 H), 7.99 (s, 1 H), 7.60 (s, 1 H), 7.42 (d, 1 H), 7.37 (s, 1 H), 7.02 (d, 1 H), 5.29 (s, 2 H), 4.59 (s, 2 H), 4.10 (s, 2 H), 1.81 (s, 3 H).

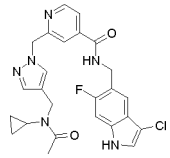
Example 303: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((4-((N-cyclopropylacetamido)methyl)-1H-pyrazol-1-yl)methyl)nicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-5-((4-((*N*-cyclopropylacetamido)methyl)-1*H*-pyrazol-1-yl)methyl)nicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((4-((N-cyclopropylacetamido)methyl)-1H-pyrazol-1-yl)methyl)nicotinamide (14 mg, 8.5% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)- pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 495.2, found 495.2. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.82 (d, 1 H), 8.44 (d, 1 H), 7.94 (s, 1 H), 7.63 (s, 1 H), 7.42 (d, 1 H), 7.38 (s, 1 H), 7.13 (s, 1 H), 7.03 (d, 1 H), 5.31 (s, 2 H), 4.60 (s, 2 H), 4.32 (s, 2 H), 2.52-2.50 (m, 1 H), 2.07 (s, 3 H), 0.80-0.71 (m, 4 H).

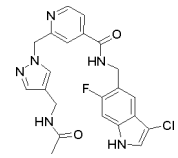
Example 304: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-((N-cyclopropylacetamido)methyl)-1H-pyrazol-1-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-((4-((*N*-cyclopropylacetamido)methyl)-1*H*-pyrazol-1-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-((N-cyclopropylacetamido)methyl)-1H-pyrazol-1-yl)methyl)isonicotinamide (50 mg, 30% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)- pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 495.2, found 495.2. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, 1 H), 7.52-7.43 (m, 4 H), 7.26 (s, 1 H), 7.07 (s, 1 H), 6.89 (d, 1 H), 5.31 (s, 2 H), 4.66 (s, 2 H), 4.34 (s, 2 H), 3.46 (s, 1 H), 2.59-2.56 (m, 1 H), 2.14 (s, 3 H), 0.88-0.85 (m, 2 H), 0.77-0.75 (m, 2 H).

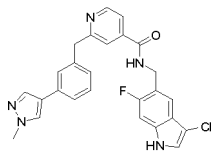
Example 305: Preparation of 2-((4-(acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-((4-(acetamidomethyl)-1*H*-pyrazol-1-yl)methyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)isonicotinamide

2-((4-(Acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (50 mg, 35% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 455.1, found 455.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.38 (s, 1 H), 9.27 (t, 1 H), 8.67 (d, 1 H), 8.13 (d, 1 H), 7.73 (d, 2 H), 7.45 (s, 1 H), 7.43 (s, 1 H), 7.38 (d, 1 H), 7.36 (s, 1 H), 7.21 (d, 1 H), 5.43 (s, 2 H), 4.59 (d, 2 H), 4.09 (d, 2 H), 1.80 (s, 3 H).

Example 306: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)isonicotinamide

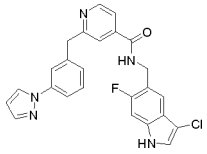


N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-(3-(1-methyl-1*H*-pyrazol-4-yl)benzyl)isonicotinamide

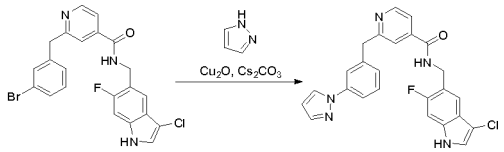
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)isonicotinamide (63 mg, 63%) was prepared as described for 2-(3-fluoro-4-formyl-phenyl)-pyrrole-1-carboxylic acid *tert*-butyl ester as a yellow solid. LRMS ($M+H^+$) m/z calculated 474.1, found 474.1.^1H NMR (CD_3OD, 400 MHz) δ 8.62 (d, 1 H), 7.91 (s, 1 H), 7.79 (s, 1 H), 7.74 (s, 1 H), 7.65 (d, 1 H), 7.52 (d, 1 H), 7.49 (s, 1 H), 7.41 (d, 1 H), 7.29 (t, 1 H), 7.25 (s, 1 H), 7.14 (d, 1 H), 7.12 (d, 1 H), 4.71 (d, 2 H), 4.23 (d, 2 H), 3.92 (s, 3 H).

Example 307, 308, 309, 310, 311, 312, 313, 314, 315, 316 were prepared as described for N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)isonicotinamide.

Example 317: Preparation of 2-(3-(1H-pyrazol-1-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

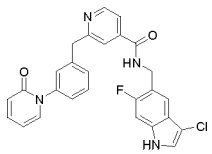


2-(3-(1*H*-pyrazol-1-yl)benzyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)isonicotinamide



To a solution of 2-(3-(1H-pyrazol-3-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5- yl)methyl)isonicotinamide (100 mg, 0.21 mmol, 1 eq) and 1H-pyrazole (18 mg, 0.26 mmol, 1.2 eq) in dry DMF (4 mL) was added Cu_2O (6.0 mg, 0.04 mmol, 0.2 eq) and Cs_2CO_3 (139 mg, 0.42 mmol, 2 eq). The mixture was stirred at 90 °C for 3 h under nitrogen atmosphere. After cooling to rt, the solvent was removed in vacuo. The residue was purified by prep-HPLC to afford 2-(3-(1H-pyrazol-1-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl) isonicotinamide (9 mg, 9%) as a white solid. LRMS ($M+H^+$) m/z calculated 461.1, found 461.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.63 (d, 1 H), 8.19 (d, 1 H), 7.76 (s, 1 H), 7.71 (d, 1 H), 7.69 (d, 1 H), 7.66 (d, 1 H), 7.60 (d, 1 H), 7.54 (d, 1 H), 7.43 (t, 1 H), 7.26 (d, 1 H), 7.25 (s, 1 H), 7.14 (d, 1 H), 6.52 (t, 1 H), 4.71 (s, 2 H), 4.30 (s, 2 H).

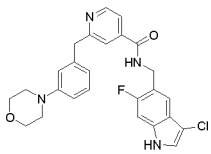
Example 318: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(2-oxopyridin-1(2H)-yl)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-(3-(2-oxopyridin-1(2*H*)-yl)benzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(2-oxopyridin-1(2H)-yl)benzyl)isonicotinamide (45 mg, 27% yields for 2 steps) was prepared as described for 2-(3-(1H-pyrazol-1-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 487.1, found 487.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.62 (d, 1 H), 7.74 (s, 1 H), 7.66-7.42 (m, 6 H), 7.35 (s, 1 H), 7.26 (d, 1 H), 7.25 (s, 1 H), 7.14 (d, 1 H), 6.61 (d, 1H), 6.46 (t, 1 H), 4.71 (s, 2 H), 4.29 (s, 2 H).

Example 319: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-morpholinobenzyl)isonicotinamide

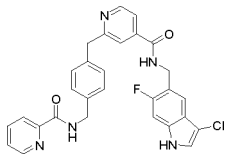


N-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)-2-(3-morpholinobenzyl)isonicotinamide

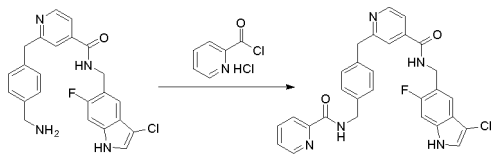
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-morpholinobenzyl)isonicotinamide (21mg, 12% yields for 2 steps) was prepared as described for N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(2-oxopyridin-1(2H)-yl)benzyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 479.2, found 479.2. ^1H NMR (CD_3OD, 400

MHz) δ 8.47 (d, 1 H), 7.56 (s, 1 H), 7.50 (dd, 1 H), 7.41 (d, 1 H), 7.13 (s, 1 H), 7.06 (t, 1 H), 6.78 (d, 1 H), 6.71 (d, 1 H), 6.66 (d, 1 H), 4.58 (s, 2 H), 4.04 (s, 2 H), 3.68 (t, 4 H), 2.98 (t, 4 H).

Example 320: Preparation of N-(4-((4-(((3-chloro-6-fluoro-1H-indol-5-yl)methyl)carbamoyl)pyridin-2-yl)methyl)benzyl)picolinamide



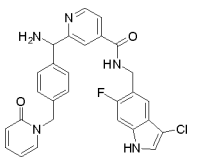
N-(4-((4-(((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)carbamoyl)pyridin-2-yl)methyl)benzyl)picolinamide



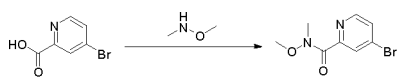
To a suspension of 2-(4-aminomethyl-benzyl)-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-isonicotinamide (100 mg, 0.20 mmol, 1.0 eq) in THF (4 mL) was added pyridine-2-carbonyl chloride (54 mg, 0.30 mmol, 1.5 eq) and Et_3N (140 mg, 1.01 mmol, 5 eq). The mixture was stirred at rt for 3 h and diluted with water. The mixture was extracted with DCM. The combined extracts were dried and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/MeOH = 40/1, v/v) to give N-(4-((4-(((3-chloro-6-fluoro-1H-indol-5-yl)methyl) carbamoyl)pyridin-2-yl)methyl)benzyl)picolinamide (45 mg, 42%) as a white solid. LRMS ($M+H^+$) m/z calculated 528.2, found 528.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.62 (t, 1 H), 8.59 (d, 1 H), 8.12 (d, 1 H), 7.96 (t, 1 H), 7.68 (s, 1 H), 7.63 (dd, 1 H), 7.55 (t, 1 H), 7.52 (d, 1 H), 7.30-7.25 (m, 4 H), 7.25 (s, 1 H), 7.14 (d, 1 H), 4.70 (s, 2 H), 4.59 (s, 2 H), 4.20 (s, 2 H).

Example 321, 322, 323, 324, 325, 326, 327 were prepared as described for N-(4-((4-(((3-chloro-6-fluoro-1H-indol-5-yl)methyl)carbamoyl)pyridin-2-yl)methyl)benzyl)picolinamide.

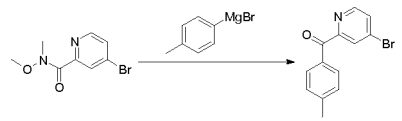
Example 328: Preparation of 2-(amino(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide.



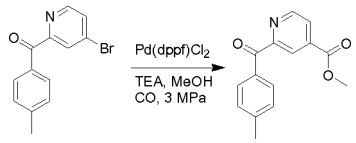
2-(amino(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)isonicotinamide



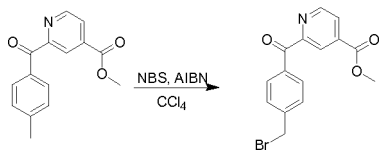
To a solution of 4-bromo-pyridine-2-carboxylic acid (5.0 g, 24.8 mmol, 1.0 eq) in DMF (10 mL) was added Et_3N (7.5 g, 74.4 mmol, 3.0 eq), O,N-dimethyl-hydroxylamine (2.41 g, 24.8 mmol, 1.0 eq) and HATU (11.3 g, 29.8 mmol, 1.2 eq). The reaction mixture was stirred at rt for 2 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated to give the crude product which was subject to silica gel chromatography (PE/EA = 5/1~2/1, v/v) to afford 4-bromo-pyridine-2-carboxylic acid methoxy-methyl-amide (6.0 g, 100%) as a white solid.



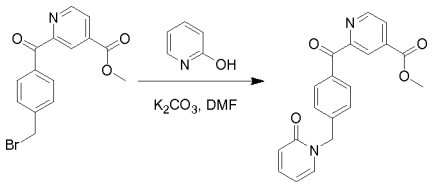
To a solution of 4-bromo-pyridine-2-carboxylic acid methoxy-methyl-amide (4.0 g, 16.3 mmol, 1.0 eq) in THF (40 mL) was added 4-methylphenyl-magnesium bromide (1.0 N, 18 mmol, 1.1 eq). The reaction mixture was stirred at rt for 0.5 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated to give the crude product which was subject to silica gel chromatography (PE/EA = 10/1~5/1, v/v) to afford (4-bromo-pyridin-2-yl)-p-tolyl-methanone (3.66 g, 82%) as a white solid.



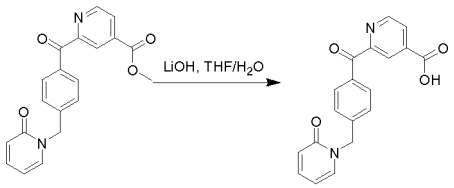
To a solution of (4-bromo-pyridin-2-yl)-p-tolyl-methanone (3.66 g, 13.3 mmol, 1.0 eq) in MeOH (40 mL) was added $Pd(dppf)Cl_2$ (0.55 g, 0.67 mmol, 0.05 eq), Et_3N (2.69 g, 26.6 mmol, 2.0 eq). The reaction mixture was stirred at 100 °C for 12 h under CO (4 MPa). Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated to give the crude product which was subject to silica gel chromatography (PE/EA = 5/1~2/1, v/v) to afford 2-(4-methyl-benzoyl)-isonicotinic acid methyl ester (3.0 g, 88%) as a white solid.



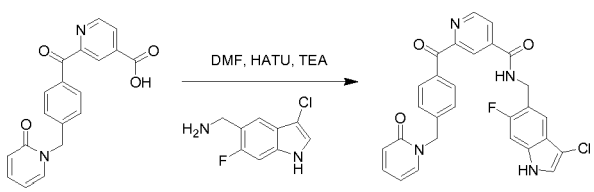
2-(4-Bromomethyl-benzoyl)-isonicotinic acid methyl ester (3.0 g, 76%) was prepared as described for 1-bromo-4-bromomethyl-5-chloro-2-fluoro-benzene as a white solid.



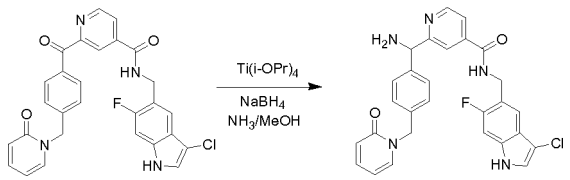
2-[4-(2-Oxo-2H-pyridin-1-ylmethyl)-benzoyl]-isonicotinic acid methyl ester (1.7 g, 54%) was prepared as described for 3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzoate as a white solid.



2-[4-(2-Oxo-2h-pyridin-1-ylmethyl)-benzoyl]-isonicotinic acid (400 mg, 100%) was prepared as described for 1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6- oxo-1,6-dihydropyridine-3-carboxylic acid as a yellow oil.

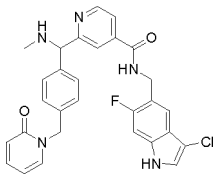


N-(3-chloro-6-fluoro-1h-indol-5-ylmethyl)-2-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzoyl]-isonicotinamide (450 mg, 77%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as a white solid.



To a solution of N-(3-chloro-6-fluoro-1h-indol-5-ylmethyl)-2-[4-(2-oxo-2H-pyridin-1-ylmethyl)-benzoyl]-isonicotinamide (100 mg, 0.19 mmol, 1.0 eq) in NH_3/MeOH (10 mL) was added Ti(i-OPr)$_4$ (110 mg, 0.38 mmol, 2.0 eq) and $NaBH_4$ (15 mg, 0.38 mmol, 2.0 eq). The reaction mixture was stirred for 12 h at rt. Water was added, and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give 2-(amino(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl) -N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (50 mg, 50%) as a white solid. LRMS (M+H$^+$) m/z calculated 516.2, found 516.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.40 (s, 1 H), 9.22 (t, 1 H), 8.58 (d, 1 H), 7.94 (s, 1 H), 7.73 (d, 1 H), 7.60 (d, 1 H), 7.51 (s, 1 H), 7.34-7.41 (m, 3 H), 7.18-7.24 (m, 3 H), 7.15 (d, 1 H), 6.38 (d, 1 H), 6.21 (t, 1 H), 5.15 (s, 1 H), 5.02 (s, 2 H), 4.59 (d, 2 H).

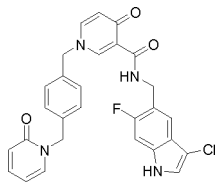
Example 329: Preparation of N-(3-chloro-6-fluoro-1h-indol-5-ylmethyl)-2-{methylamino-[4-(2-oxo-2H-pyridin-1-ylmethyl)-phenyl]-methyl}-isonicotinamide



N-(3-chloro-6-fluoro-1h-indol-5-ylmethyl)-2-{methylamino
-[4-(2-oxo-2H-pyridin-1-ylmethyl)-phenyl]-methyl}-isonicotinamide

N-(3-chloro-6-fluoro-1h-indol-5-ylmethyl)-2-{methylamino-[4-(2-oxo-2H-pyridin-1-ylmethyl)-phenyl]-methyl}-isonicotinamide (36 mg, 30%) was prepared as described for 2-(amino(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide as a white solid. LRMS (M+H$^+$) m/z calculated 530.2, found 530.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.23 (s, 1 H), 9.22 (t, 1 H), 8.58 (s, 1 H), 7.94 (s, 1 H), 7.92 (s, 1 H), 7.74 (s, 1 H), 7.72 (s, 1 H), 7.34-7.51 (m, 5 H), 7.18-7.24 (m, 3 H), 6.37 (d, 1 H), 6.20 (s, 1 H), 5.15 (s, 1 H), 5.02 (s, 2 H), 4.79 (s, 1 H), 4.59 (s, 2 H), 2.22 (s, 3 H).

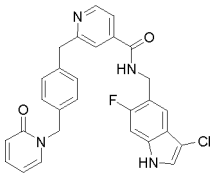
Example 330: Preparation of 4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1,4-dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1H-indol-5-ylmethyl)-amide



4-(2-oxo-2H-pyridin-1-ylmethyl)-benzyl]-1,4-dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1H-indol-5-ylmethyl)-amide

4-(2-Oxo-2h-pyridin-1-ylmethyl)-benzyl]-1,4-dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1H-indol-5-ylmethyl)-amide (80 mg, 27.2%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as a white solid. LRMS ($M+H^+$) m/z calculated 517.1, found 517.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 10.62 (t, 1 H), 8.64 (t, 1 H), 7.91 (d, 1 H), 7.76 (d, 1 H), 7.50 (s, 1 H), 7.39-7.43 (m, 2 H), 7.28-7.34 (m, 4 H), 7.22 (d, 1 H), 6.39-6.44 (m, 2 H), 6.20-6.24 (m, 1 H), 5.26 (s, 2 H), 5.08 (s, 2 H), 4.60 (d, 2 H).

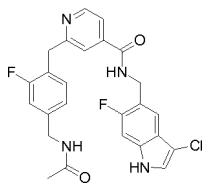
Example 331: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide (110 mg, 55% yields for 2 steps) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 501.1, found 501.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.36 (s, 1 H), 9.18 (t, 1 H), 8.54 (d, 1 H), 7.88 (s, 1 H), 7.75 (dd, 1 H), 7.48 (d, 1 H), 7.46 (d, 1 H), 7.42 (d, 1 H), 7.39 (d, 1 H), 7.26-7.18 (m, 5 H), 6.40 (d, 1 H), 6.21 (t, 1 H), 5.05 (s, 2 H), 4.60 (d, 2 H), 4.05 (s, 2 H).

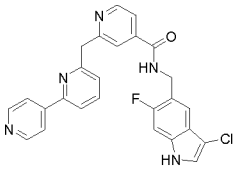
Example 333: Preparation of 2-(4-(acetamidomethyl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



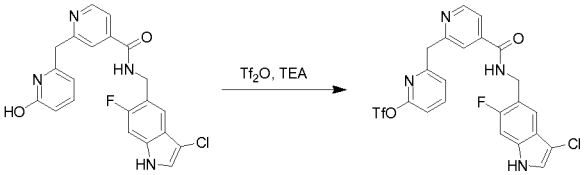
2-(4-(acetamidomethyl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

2-(4-(Acetamidomethyl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (63 mg, 43%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 483.1, found 483.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.56 (s, 1 H), 9.34 (s, 1 H), 8.58-8.60 (m, 1 H), 8.42 (d, 1 H), 7.66 (d, 2 H), 7.42-7.7.49 (m, 2 H), 7.21-7.29 (m, 2 H), 7.02 (d, 2 H), 4.57 (d, 2 H), 4.21 (d, 2 H), 4.14 (d, 2 H), 1.85 (s, 3 H).

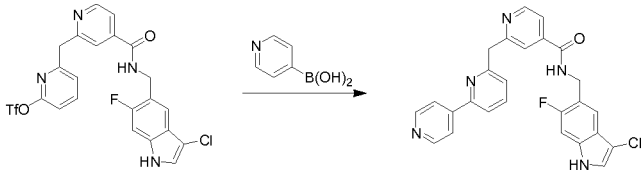
Example 334: Preparation of 2-([2,4'-bipyridin]-6-ylmethyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-([2,4'-bipyridin]-6-ylmethyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl) methyl)isonicotinamide

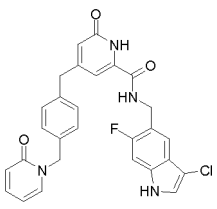


To a solution of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-(6-hydroxy- pyridin-2-ylmethyl)-isonicotinamide (98 mg, 0.24 mmol, 1 eq) in DCM (5 mL) was added Tf_2O (82 mg, 0.29 mmol, 1.5 eq) and Et_3N (50 mg, 0.48 mmol, 2 eq) at 0 °C. The mixture was stirred at rt for 5 h and concentrated. The residue was purified by flash chromatography on a silica gel column (DCM/MeOH = 20/1, v/v) to give trifluoro-methanesulfonic acid 6-{4-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-2-ylmethyl}-pyridin-2-yl ester (91 mg, 70%) as a white solid.

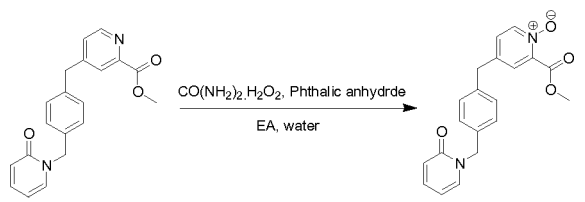


To a solution of trifluoro-methanesulfonic acid 6-{4-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-2-ylmethyl}-pyridin-2-yl ester (91 mg, 0.17 mmol, 1 eq) in dioxane (4 mL) and water (1 mL) was added pyridine-4-boronic acid (25 mg, 0.20 mmol, 1.2 eq), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 0.1eq), and Na_2CO_3 (54 mg, 0.51 mmol, 3 eq) . The mixture was stirred at 90 °C for 2 h under nitrogen atmosphere. After cooling to rt the solvent was removed in vacuo. The residue was purified by prep-HPLC to afford 2-([2,4'-bipyridin]-6-ylmethyl)-N-((3-chloro-6-fluoro-1H -indol-5-yl)methyl)isonicotinamide (10 mg, 13%) as an off-white solid. LRMS ($M+H^+$) m/z calculated 472.1, found 472.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.51 (d, 1 H), 8.47 (d, 1 H), 8.46 (d, 1 H), 7.92 (d, 1 H), 7.91 (d, 1 H), 7.76 (s, 2 H), 7.75 (d, 1 H), 7.56 (dd, 1 H), 7.41 (d, 1 H), 7.30 (t, 1 H), 7.12 (s, 1 H), 7.01 (d, 1 H), 4.60 (s, 2 H), 4.37 (s, 2 H).

Example 335: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-4-(4-((2-oxopyridin -1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-2-carboxamide



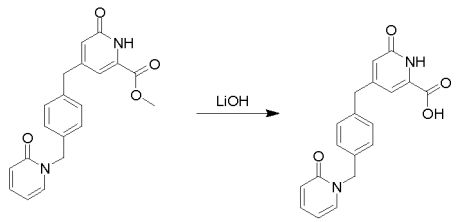
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-4-(4-((2-oxopyridin -1(2H)-yl) methyl)benzyl)-1,6-dihydropyridine-2-carboxamide



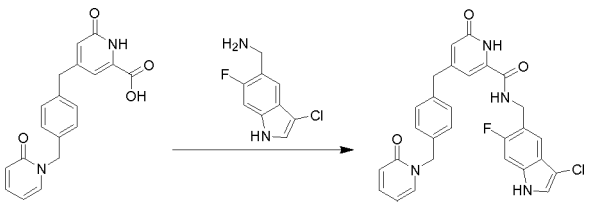
To a mixture of methyl 4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinate (500 mg, 1.5 mmol, 1.0 eq) in EA/water (10 mL/0.5 mL) was added $CO(NH_2)_2.H_2O_2$ (422 mg, 4.5 mmol, 3.0 eq) followed by phthalic anhydrde (666 mg, 4.5 mmol, 3.0 eq) portionwise at 0 °C. The resultant mixture was heated to 45 °C and kept stirring for 4 h. The reaction mixture was quenched with 10% of Na_2SO_4 (1.5 eq), and extracted with DCM. The organic layer was washed with sat.Na_2CO_3, followed by brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (DCM~DCM/MeOH = 20/1, v/v) to give 2-(methoxycarbonyl)-4-(4-((2-oxopyridin-1(2H)-yl) methyl)benzyl)pyridine 1-oxide (100 mg, 19%) as a yellow solid. LRMS ($M+H^+$) m/z calculated 351, found 351.



The mixture of 2-(methoxycarbonyl)-4-(4-((2-oxopyridin-1(2H)-yl) methyl)benzyl)pyridine 1-oxide (300 mg, 0.86 mmol, 1.0 eq) in Ac_2O (5 mL) was kept stirring for 1 h at 130 °C. And then the solvent was removed. The residue was dissolved in DCM (30 mL), washed with sat.$NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in MeOH (5 mL). To the mixture was added K_2CO_3 (237 mg), and the reaction mixture was kept stirring for 3 h. The reaction mixture was concentrated, and the residue was purified by prep-HPLC to give methyl 6-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-2-carboxylate (150 mg, 50%) as a yellow solid. LRMS ($M+H^+$) m/z calculated 351, found 351.



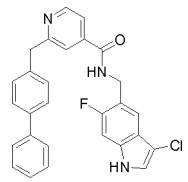
6-Oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl) -1,6-dihydropyridine-2-carboxylic acid (200 mg, crude) was prepared as described for 1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid. LRMS ($M+H^+$) m/z calculated 337, found 337.



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-2-carboxamide (10 mg, 9%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin -2-ylmethyl)-carbamic acid *tert*-butyl ester as an off-white solid. LRMS ($M+H^+$) m/z calculated 517, found 517. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.43 (s, 1 H), 9.21 (t, 1 H), 8.56 (d, 1 H), 8.03 (s, 1 H), 7.75 (d, 1 H), 7.59 (d, 1 H), 7.48 (d, 1 H), 7.39-7.41 (m, 2 H),

7.35-7.38 (m, 2 H), 7.19-7.26 (m, 3 H), 6.38 (d, 1 H), 6.25 (d, 1 H), 6.20 (t, 1 H), 5.80 (d, 1 H), 5.06 (s, 2 H), 4.59 (d, 2 H).

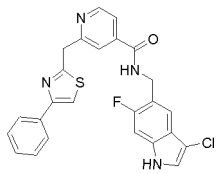
Example 336: Preparation of 2-([1,1'-biphenyl]-4-ylmethyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl) methyl)isonicotinamide



2-([1,1'-biphenyl]-4-ylmethyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl) methyl)isonicotinamide

2-([1,1'-Biphenyl]-4-ylmethyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl) isonicotinamide (47 mg, 30%) was prepared as described for (5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamic acid *tert*-butyl ester as an off-white solid. LRMS ($M+H^+$) m/z calculated 470, found 470. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.40 (s, 1 H), 9.25 (t, 1 H), 8.64 (d, 1 H), 7.56 (s, 1 H), 7.57-7.65 (m, 5 H), 7.50 (d, 1 H), 7.42-7.46 (m, 3 H), 7.32-7.38 (m, 3 H), 7.22 (d, 1 H), 4.59 (d, 2 H), 4.19 (s, 2 H).

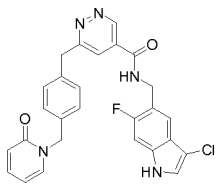
Example 337: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-phenylthiazol-2-yl)methyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-phenylthiazol-2-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-phenylthiazol-2-yl)methyl)isonicotinamide (40 mg, 37.2%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 477.1, found 477.1. ^{1}HNMR (DMSO-d_6, 300 MHz) δ 11.42 (s, 1 H), 9.31 (t, 1 H), 8.71 (d, 1 H), 7.99 (s, 1 H), 9.30 (d, 3 H), 7.73-7.75 (m, 1 H), 7.22-7.52 (m, 6 H), 4.62 (d, 4 H).

Example 338: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridazine-4-carboxamide

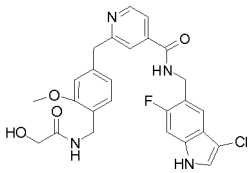


N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-(4-((2-oxopyridin -1(2H)-yl)methyl)benzyl)pyridazine-4-carboxamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridazine-4-carboxamide (18 mg, 22.36%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 501.7, found 501.7. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.25 (s, 1 H), 7.75 (s, 1 H), 7.51 (d, 1 H), 7.35-7.39 (m, 2 H), 7.12 (t, 5 H), 6.99 (d, 1 H), 6.41 (d, 1 H), 6.22 (t, 1 H), 5.00 (s, 2 H), 4.55 (s, 2 H), 4.21 (s, 2 H).

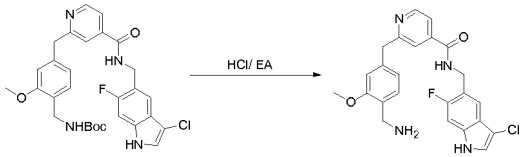
Example 339: Preparation of N-(3-Chloro-6-fluoro-1H-indol-5-ylmethyl)-2-{4-[(2-hydroxy-acetylamino)-

methyl]-3-methoxy-benzyl}-isonicotinamide

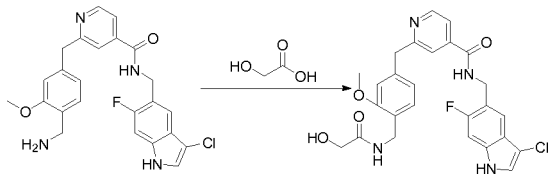


N-(3-Chloro-6-fluoro-1*H*-indol-5-ylmethyl)-2-{4-[(2-hydroxy-acetylamino)-methyl]-3-methoxy-benzyl}-isonicotinamide

(4-{4-[(3-Chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-2-ylmethyl}-2-methoxy-benzyl)-carbamic acid *tert*-butyl ester (0.54 mg, 75%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3- ylmethyl]-nicotinamide.

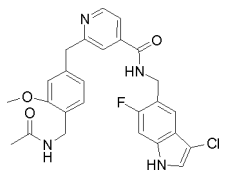


The mixture of (4-{4-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]-pyridin-2-ylmethyl}-2-methoxy-benzyl)-carbamic acid *tert*-butyl ester (0.54 g, 1 mmol) with HCl/EA was stirred at rt for 3 h. Then it was concentrated in *vacuum* to get 2-(4-aminomethyl-3-methoxy-benzyl)-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-isonicotinamide hydrochloride salt (0.5 g, 100%)



To a solution of compound 2-(4-aminomethyl-3-methoxy-benzyl)-N-(3-chloro-6- fluoro-1H-indol-5-ylmethyl)-isonicotinamide hydrochloride salt (0.15 g, 0.2 mmol, 1 eq) in DMF (5 mL) was added hydroxy-acetic acid (0.023 g, 0.3 mmol, 1.5 eq), HOBT (0.033 g, 0.25 mmol, 1.2 eq), EDCI (0.048 g, 0.25 mmol, 1.2 eq) and Et_3N (0.083 g, 0.82 mmol, 4 eq). The mixture was stirred at rt overnight. The residue was purified by chromatography on a silica gel column (DCM/MeOH = 20/1, v/v) to give N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-{4- [(2-hydroxy-acetylamino)-methyl]-3-methoxy-benzyl}-isonicotinamide (25 mg, 16%) as a white solid. LRMS ($M+H^+$) m/z calculated 510.1, found 510.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.50 (s, 1 H), 9.40 (t, 1 H), 8.70 (s, 1 H), 8.60 (s, 1 H), 8.04 (s, 3 H), 7.86 (d, 2 H), 7.51 (d, 1 H), 7.46 (d, 1 H), 7.24 (d, 1 H), 7.15 (d, 1 H), 7.04(s, 1 H), 6.88(d, 1 H), 4.58 (d, 2 H), 4.24 (s, 4 H), 3.89 (s, 4 H), 3.56 (m, 3 H).

Example 340: Preparation of 2-(4-(acetamidomethyl)-3-methoxybenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

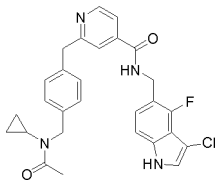


2-(4-(acetamidomethyl)-3-methoxybenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

2-[4-(Acetylamino-methyl)-3-methoxy-benzyl]-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-isonicotinamide (7 mg, 7%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-{4-[(2-hydroxy-acetylamino)-methyl]-3-methoxy-benzyl}-isonicotinamide. LRMS ($M+H^+$) m/z calculated 495.2, found

495.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.50 (s, 1 H), 9.20 (t, 1 H), 8.70 (d, 1 H), 8.10 (s, 1 H), 7.69 (s, 1 H), 7.63 (t, 1H), 7.51 (d, 1 H), 7.45 (d, 1 H), 7.24 (d, 1 H), 7.05 (d, 1 H), 6.92 (s, 1 H), 6.81 (d, 1 H), 4.58 (d, 2 H), 4.15 (s, 4 H), 3.75 (s, 3 H), 1.83 (s, 3 H).

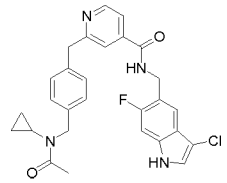
Example 341: Preparation of 2-{4-[(Acetyl-cyclopropyl-amino)-methyl]-benzyl}-N-(3-chloro-4-fluoro-1H-indol-5-ylmethyl)-isonicotinamide



2-{4-[(Acetyl-cyclopropyl-amino)-methyl]-benzyl}-N-(3-chloro-4-fluoro-1H-indol-5-ylmethyl)-isonicotinamide

N-({4-[(4-{N-[(3-chloro-4-fluoroindol-5-yl)methyl]carbamoyl}(2-pyridyl))methyl]phenyl}methyl)-N-cyclopropylacetamide (11 mg, 7%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS (M+H$^+$) m/z calculated 505.2, found 505.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.58 (s, 1 H), 9.22 (t, 1 H), 8.62(d, 1 H), 7.73 (s, 1 H), 7.65 (m, 1 H), 7.50 (d, 1H), 7.22 (m, 3 H), 7.12 (m, 3 H), 4.56 (d, 2 H), 4.43 (s, 2 H), 4.12 (s, 2 H), 2.61(t, 1 H), 2.15 (d, 3 H), 0.75 (m, 3 H).

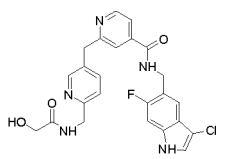
Example 342: Preparation of 2-{4-[(acetyl-cyclopropyl-amino)-methyl]-benzyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-isonicotinamide



2-{4-[(Acetyl-cyclopropyl-amino)-methyl]-benzyl}-*N*-(3-chloro-6-fluoro-1*H*-indol-5-ylmethyl)-isonicotinamide

2-{4-[(Acetyl-cyclopropyl-amino)-methyl]-benzyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-isonicotinamide (27 mg, 18%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS (M+H$^+$) m/z calculated 505.2, found 505.2. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.58 (s, 1 H), 9.22 (t, 1 H), 8.62(d, 1 H), 7.75 (s, 1 H), 7.67(m, 1 H), 7.50 (d, 1H), 7.45 (m, 1 H), 7.23 (m, 3 H), 7.12 (m, 2 H), 4.56 (d, 2 H), 4.43 (s, 2 H), 4.12 (s, 2 H), 2.61 (t, 1 H), 2.15 (d, 3 H), 0.75 (m, 4 H).

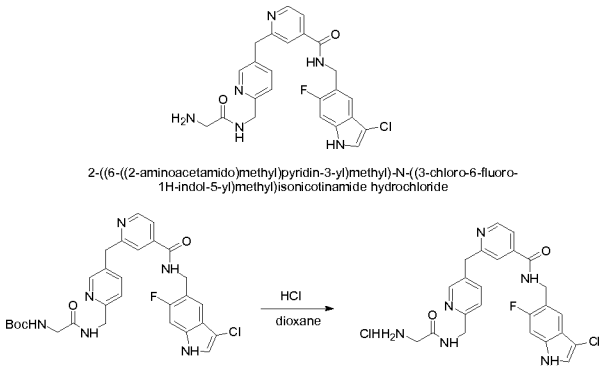
Example 343: Preparation of N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-{6-[(2-hydroxy-acetylamino)-methyl]-pyridin-3-ylmethyl}-isonicotinamide



N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-2-{6-[(2-hydroxy-acetylamino)-methyl]-pyridin-3-ylmethyl}-isonicotinamide

N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-{6-[(2-hydroxy-acetylamino)-methyl]-pyridin-3-ylmethyl}-nicotinamide (20 mg, 35.3%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin-2-yl)-pyridin-3-ylmethyl]-nicotinamide as yellow oil. LCMS ($M+H^+$) m/z calculated 482.1, found 482.1. ^1H NMR (CD_3OD, 400 MHz) δ 8.61 (d, 1 H), 8.46 (d, 1 H), 7.74-7.71 (m, 2 H), 7.65 (d, 1 H), 7.54 (d, 1 H), 7.32 (d, 1 H), 7.25 (s, 1 H), 7.14 (d, 1 H), 4.72 (s, 2 H), 4.54 (s, 2 H), 4.24 (s, 2 H), 4.05 (d, 2 H).

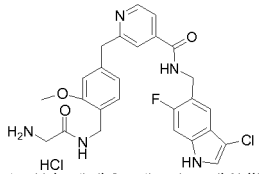
Example 344: Preparation of 2-((6-((2-aminoacetamido)methyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-((6-((2-aminoacetamido)methyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide hydrochloride

The mixture of {[(5-{5-[(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-carbamoyl]- pyridin-3-ylmethyl}-pyridin-2-ylmethyl)-carbamoyl]-methyl}-carbamic acid *tert*-butyl ester (80 mg, 0.14 mmol, 1.0 eq) in DCM (10 mL) was added HCl (4 N in dioxane, 3 mL). The mixture was stirred at rt for 1 h. The mixture was evaporated in vacuum to residue, which was purified by pre-HPLC (MeCN/H_2O from 5/100 to 95/100, v/v) to give of 5-{6-[(2-amino-acetylamino)-methyl]-pyridin-3-ylmethyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide (40 mg, 59.5 %) as yellow solid. LRMS ($M+H^+$) m/z calculated 481.1, found 481.1. ^1H NMR (Methanol-d_4, 400 MHz) δ 8.91-8.88 (m, 2 H), 8.60 (d, 1 H), 8.16-8.14 (m, 2 H), 8.05 (d, 1 H), 7.56 (d, 1 H), 7.27 (s, 1 H), 7.16 (d, 1 H), 4.76 (s, 2 H), 4.71 (s, 2 H), 3.89 (s, 2 H), 3.37 (s, 2 H).

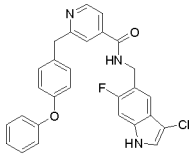
Example 345: Preparation of 2-(4-((2-aminoacetamido)methyl)-3-methoxybenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-(4-((2-aminoacetamido)methyl)-3-methoxybenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide hydrochloride

2-(4-((2-Aminoacetamido)methyl)-3-methoxybenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide hydrochloride (30 mg, 29%) was prepared as described for 5-{6-[(2-amino-acetylamino)-methyl]-pyridin-3-ylmethyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide. LRMS ($M+H^+$) m/z calculated 510.2, found 510.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.50 (s, 1 H), 9.20 (t, 1 H), 8.70 (d, 1 H), 8.10 (s, 1 H), 7.91 (t, 1 H), 7.69 (s, 1 H), 7.63 (t, 1H), 7.51 (s, 1 H), 7.45 (d, 1 H), 7.24 (d, 1 H), 7.05 (d, 1 H), 6.92 (s, 1 H), 6.81 (d, 1 H), 5.48 (t, 1 H), 4.58 (d, 2 H), 4.23 (d, 2 H), 4.12 (d, 2 H), 3.83 (d, 2 H), 3.77 (s, 3 H).

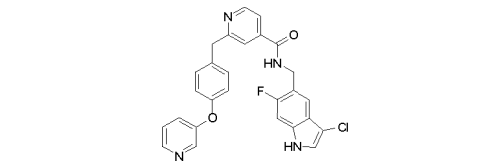
Example 346: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-phenoxybenzyl)isonicotinamide



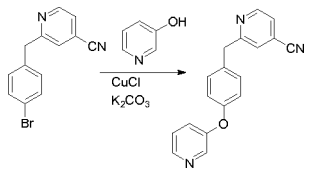
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-phenoxybenzyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-phenoxybenzyl)isonicotinamide (25 mg, 41% yields for 2 steps) was prepared as described for 5-{6-[(2-amino-acetylamino)-methyl]-pyridin-3-ylmethyl}-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 486.1, found 486.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (s, 1 H), 9.24 (t, 1 H), 8.64 (d, 1 H), 7.72 (s, 1 H), 7.64 (d, 1 H), 7.50-7.21 (m, 7 H), 7.70-6.91 (m, 5 H), 4.60 (d, 1 H), 4.12 (s, 1 H)

Example 347: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyridin-3-yloxy)benzyl)isonicotinamide

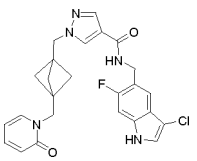


N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyridin-3-yloxy)benzyl)isonicotinamide



N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyridin-3-yloxy)benzyl)isonicotinamide (37 mg, 20% yields for 2 steps) was prepared as described for N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-phenoxybenzyl)isonicotinamide as a white solid. LRMS ($M+H^+$) m/z calculated 487.1, found 487.1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66-8.64 (d, 1 H), 8.41-8.33 (m, 3 H), 7.62-7.60 (d, 1 H), 7.50 (s, 1 H), 7.43-7.41 (d, 1 H), 7.28-7.23 (m, 3 H), 7.17-7.16 (d, 1 H), 7.08-7.05 (d, 1 H), 6.95-6.93 (d, 2 H), 6.52 (s, 1 H), 4.77-4.76 (d, 2 H), 4.18 (s, 2 H)

Example 348: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-((3-((2-oxopyridin-1(2H)-yl)methyl)bicyclo[1.1.1]pentan-1-yl)methyl)-1H-pyrazole-4-carboxamide

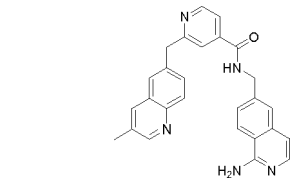


N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-((3-((2-oxopyridin-1(2H)-yl)methyl)bicyclo[1.1.1]pentan-1-yl)methyl)-1H-pyrazole-4-carboxamide

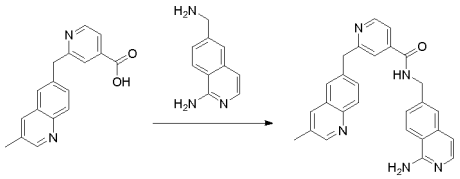
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-((3-((2-oxopyridin-1(2H)-yl)methyl)bicyclo[1.1.1]pentan-1-yl)methyl)-1H-pyrazole-4-carboxamide (55 mg, 42%) was prepared as described for N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-5-[6-(5-oxo-pyrrolidin -2-yl)-pyridin-3-ylmethyl]-nicotinamide. LRMS ($M+H^+$) m/z calculated 480.1, found 480.1. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.37 (s, 1 H), 8.53 (t, 1 H), 8.09 (s, 1 H),

7.85 (s, 1 H), 7.50-7.47 (m, 2 H), 7.43-7.41 (m, 1 H), 7.32-7.38 (m, 1 H), 7.22-7.20 (d, 1 H), 6.35-6.32 (d, 1 H), 6.15-6.14 (t, 1 H), 4.51-4.50 (d, 2 H), 4.19 (s, 2 H), 3.97 (s, 2 H), 1.47 (s, 6 H).

Example 349: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide

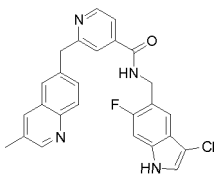


N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide



To a solution of 2-(3-methyl-quinolin-6-ylmethyl)-isonicotinic acid (150 mg, crude) in DMF (15 mL) was added 6-Aminomethyl-isoquinolin-1-ylamine (62 mg, 0.36 mmol, 1.0 eq) followed by EDCI (104 mg, 0.54 mmol, 1.5 eq), HOBT (73 mg, 0.54 mmol, 1.5 eq) and TEA (109 mg, 1.08 mmol, 3.0 eq). The reaction mixture was heated to 40°C kept stirring for overnight. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl) isonicotinamide (30 mg, 19%) as a white solid. LRMS ($M+H^+$) m/z calculated 434, found 434. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.40 (t, 1 H), 8.71 (s, 1 H), 8.67 (d, 1 H), 8.13 (d, 1 H), 8.07 (s, 1 H), 7.90 (d, 1 H), 7.75-7.80 (m, 3 H),7.68 (d, 1 H), 7.62 (d, 1 H), 7.54 (s, 1 H), 7.49 (d, 1 H), 6.84 (d, 1 H), 6.77 (s, 2 H), 4.60 (d, 2 H), 4.35 (s, 2 H), 2.46 (s, 3 H).

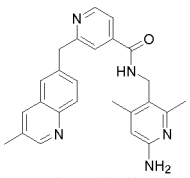
Example 350: Preparation of N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide



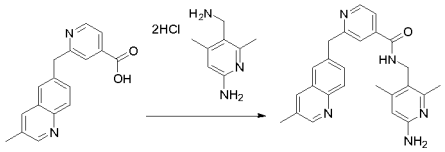
N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide (30 mg, 18%) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide as a yellow solid. LRMS (M+H+) m/z calculated 459, found 459. 1H NMR (DMSO-d_6, 300 MHz) δ 11.42 (br, 1 H), 9.25 (t, 1 H), 8.71 (s, 1 H), 8.65 (d, 1 H), 8.05 (s, 1 H), 7.89 (d, 1 H), 7.76 (d, 2 H), 7.60-7.66 (m, 2 H),7.51 (d, 1 H), 7.43 (d, 1 H), 7.22 (d, 2 H), 4.58 (d, 2 H), 4.34 (s, 2 H), 2.46 (s, 3 H).

Example 351: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide

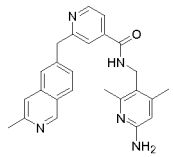


N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide



To a solution of 2-(3-methyl-quinolin-6-ylmethyl)-isonicotinic acid (150 mg, crude) in DMF (15 mL) was added 5-aminomethyl-4,6-dimethyl-pyridin-2-ylamine dihydrochloride (400 mg, crude) followed by EDCI (104 mg, 0.54 mmol, 1.5 eq), HOBT (73 mg, 0.54 mmol, 1.5 eq) and TEA (109 mg, 1.08 mmol, 3.0 eq). The reaction mixture was heated to 40 ºC kept stirring for overnight. Water was added, and the mixture was extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC to give N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide (25 mg, 17%) as a yellow solid. LRMS ($M+H^+$) m/z calculated 412, found 412. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.71 (s, 1 H), 8.65 (t, 1 H), 8.60 (d, 1 H), 8.06 (s, 1 H), 7.89 (d, 1 H), 7.74 (d, 2 H),7.60 (d, 2 H), 6.10 (s, 1 H), 5.70 (s, 2 H), 4.32 (s, 4 H), 2.46 (s, 3 H), 2.29 (s, 3 H), 2.15 (s, 3 H).

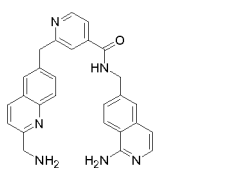
Example 352: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide



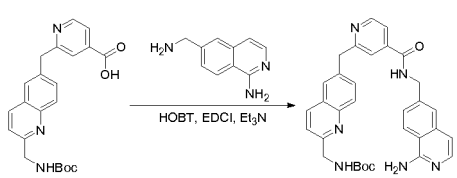
N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide (29 mg, 21% yields for 2 steps) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 412.2, found 412.2. ^1H NMR (CD_3OD, 400 MHz) δ 9.05 (s, 1 H), 8.61 (d, 1 H), 7.96 (s, 1 H), 7.73 (s, 1 H), 7.69 (s, 1 H), 7.62 (dd, 1 H), 7.55 (s, 1 H), 7.52 (d, 1 H), 6.30 (s, 1 H), 4.49 (s, 2 H), 4.38 (s, 2 H), 2.64 (s, 3 H), 2.39 (s, 3 H), 2.26 (s, 3 H).

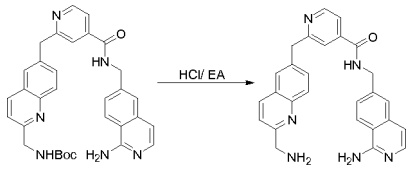
Example 353: Preparation of N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide



N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide

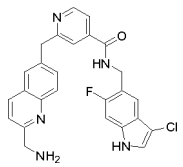


(6-{4-[(1-Amino-isoquinolin-6-ylmethyl)-carbamoyl]-pyridin-2-ylmethyl}-quinolin-2-ylmethyl)-carbamic acid tert-butyl ester (70 mg, 35%) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide.



To a solution of (6-{4-[(1-amino-isoquinolin-6-ylmethyl)-carbamoyl]-pyridin-2-ylmethyl}-quinolin-2-ylmethyl)-carbamic acid tert-butyl ester (80 mg, 0.13 mmol) in EA (1 mL) was added HCl/EA solution. The mixture was stirred at rt for 1 h. The precipitate was collected by filtration to give N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl) isonicotinamide (50 mg, 66%) as an off-white solid. LRMS ($M+H^+$) m/z calculated 449.2, found 449.2. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.51 (s, 1 H), 10.05 (s, 1 H), 9.25 (br, 1 H), 8.88 (d, 1 H), 8.63-8.62 (m, 4 H), 8.45 (d, 1 H), 8.19 (s, 1 H), 8.09-8.01 (m, 3 H), 7.89 (d, 1 H), 7.85 (s, 1 H), 7.73-7.64 (m, 4 H), 7.20 (d, 1 H), 4.69 (d, 2 H), 4.59 (s, 2 H), 4.39 (t, 2 H).

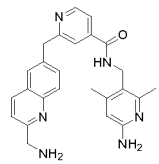
Example 354: Preparation of 2-((2-(aminomethyl)quinolin-6-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide



2-((2-(aminomethyl)quinolin-6-yl)methyl)-*N*-((3-chloro-6-fluoro-1*H*-indol-5-yl)methyl)isonicotinamide

2-((2-(Aminomethyl)quinolin-6-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide (60 mg, 79%) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 474.1, found 474.1. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.53 (s, 1 H), 9.58 (s, 1 H), 8.83 (d, 1 H), 8.60 (br, 1 H), 8.43 (d, 1 H), 8.10 (d, 1 H), 8.02-8.00 (m, 3 H), 7.85 (d, 1 H), 7.62 (d, 1 H), 7.51 (s, 1 H), 7.47 (d, 1 H), 7.44 (d, 1 H), 7.31 (s, 1 H), 7.24 (d, 1 H), 7.20 (d, 1 H), 4.60 (d, 2 H), 4.57 (s, 2 H), 4.40 (q, 2 H).

Example 355: Preparation of N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide



N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide (35 mg, 53%) was prepared as described for N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide. LRMS ($M+H^+$) m/z calculated 427.2, found 427.2. ^1H NMR (CD_3OD, 400 MHz) δ 8.99 (d, 1 H), 8.69 (d, 1 H), 8.39 (s, 1 H), 8.35 (d, 1 H), 8.25 (d, 1 H), 8.16 (s, 1 H), 7.98 (d, 1 H), 7.80 (d, 1 H), 6.74 (s, 1 H), 4.82 (s, 2 H), 4.63 (s, 2 H), 4.59 (s, 2 H), 2.63 (s, 3 H), 2.50 (s, 3 H).

Example 356:

Illustrative compounds of the present invention are listed in **Table 1**. **Table 2** shows IC_{50} values for the compounds in **Table 1** against human plasma kallikrein. The scale utilized in **Table 2** is as follows: +++ less than 100 nM, ++ between 100 and 1000 nM, and + greater than 1000 nM.

Table 1. Illustrative Compounds of the Present Invention

Compound No.	Chemical Name
C01	N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamide
C02	N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)benzamide
C03	N-((5-chloro-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)nicotinamide
C04	N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzenesulfonamide
C05	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridine-3-sulfonamide
C06	N-((5-chloro-1H-indazol-3-yl)methyl)-5-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)amino)pyridine-3-sulfonamide
C07	N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide
C08	N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indazole-3-carboxamide
C09	N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide
C10	2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetic acid
C11	N-((5-chloro-1H-indazol-3-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperazine-2-carboxamide
C12	methyl 2-(5-chloro-3-((1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamido)methyl)-1H-indazol-1-yl)acetate
C13	N-((5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-indole-3-carboxamide
C14	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C15	N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide
C16	N-((5-chloro-1H-indazol-3-yl)methyl)-5-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-4,5-dihydropyrazine-2-carboxamide
C17	N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyrazine-2-carboxamide
C18	N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxamide
C19	N-((5-chloro-1H-indazol-3-yl)methyl)-1-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)pyrrolidine-3-carboxamide
C20	N-((5-chloro-1H-indazol-3-yl)methyl)-3-(N-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamido)benzamide

C21	N-((5-chloro-1H-indazol-3-yl)methyl)-3-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)benzamide
C22	N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)piperidine-3-carboxamide
C23	N-((5-chloro-1H-indazol-3-yl)methyl)-3-((4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)sulfonyl)benzamide
C24	N-(4-aminobenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C25	N-((5-chlorobenzo[b]thiophen-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C26	methyl 2-(5-chloro-1H-indazol-3-yl)-2-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)benzamido)acetate
C27	N-(4-(aminomethyl)benzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C28	N-((5-chloro-1H-indazol-3-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide
C29	N-((6-aminopyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C30	N-((5-chloro-1H-indazol-3-yl)methyl)-3-(hydroxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide
C31	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C32	5-(4-carbamoylbenzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide
C33	N-((5-chloro-1H-indazol-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C34	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)phenoxy)nicotinamide
C35	methyl 2-(5-chloro-1H-indazol-3-yl)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)acetate
C36	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxopyrrolidin-1-yl)benzyl)nicotinamide
C37	N-((6-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C38	N-((5-chloro-1H-indol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C39	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C40	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C41	N-((5-chloro-1-methyl-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C42	N-((5-chloro-1H-indazol-3-yl)methyl)-3-(methoxy(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide
C43	N-((5-chloro-1H-indazol-3-yl)methyl)-3-(1-hydroxy-1-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)ethyl)benzamide
C44	N-((5-chloro-1H-indazol-3-yl)methyl)-3-(difluoro(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)benzamide
C45	N-((1H-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C46	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxopyridin-1(2H)-yl)benzyl)nicotinamide

C47	2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(3-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)phenyl)acetic acid
C48	N-((1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C49	N-((1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C50	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C51	N-((6-amino-2-methylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C52	N-(3-chlorobenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C53	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((3-oxomorpholino)methyl)benzyl)nicotinamide
C54	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C55	5-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide
C56	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C57	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C58	N-((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C59	N-((3-chloro-1H-indol-6-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C60	N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C61	N-((5-amino-3-methylpyrazin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C62	N-((5-aminopyridin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C63	N-(4-chloro-2-methylbenzyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C64	N-((5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide
C65	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C66	N-((6-amino-4-methylpyridin-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C67	N-((3-aminobenzo[d]isoxazol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C68	N-((5-chloro-1H-indazol-3-yl)methyl)-1-(2,5-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C69	N-((5-chloro-1H-indazol-3-yl)methyl)-1-(2,5-dichloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C70	N-((5-chloro-1H-indazol-3-yl)methyl)-1-(5-chloro-2-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C71	methyl 2-(5-chloro-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate
C72	2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid

C73	N-(1-(5-chloro-1H-indazol-3-yl)ethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C74	2-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)acetic acid
C75	N-((6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C76	1-(4-((4-(1-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2,2,2-trifluoroethyl)-1H-pyrazol-1-yl)methyl)benzyl)pyridin-2(1H)-one
C77	N-((3-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C78	5-chloro-N-(2,2,2-trifluoro-1-(1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1H-pyrazol-4-yl)ethyl)-1H-indazole-3-carboxamide
C79	N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C80	N-((1-(3-amino-3-oxopropyl)-5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide
C81	3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoic acid
C82	ethyl 3-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoate
C83	N-((3-chloro-6-methyl-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C84	N-((6-methyl-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C85	N-((1-(2-amino-2-oxoethyl)-5-chloro-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide
C86	methyl 2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetate
C87	2-(((5-chloro-1H-indazol-3-yl)methyl)amino)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid
C88	2-(5-chloro-1H-indazole-3-carboxamido)-2-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridin-3-yl)acetic acid
C89	5-(4-((1H-pyrazol-1-yl)methyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide
C90	N-(1-(5-chloro-1H-indazol-3-yl)ethyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide
C91	N-((5-chloro-1-(2-hydroxyethyl)-1H-indazol-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide
C92	methyl 2-(5-chloro-3-((5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamido)methyl)-1H-indazol-1-yl)acetate
C93	ethyl 3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoate
C94	3-(5-chloro-3-((5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)methyl)-1H-indazol-1-yl)propanoic acid
C95	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopiperazin-1-yl)methyl)benzyl)nicotinamide
C96	N-((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C97	N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C98	5-(4-(2-amino-2-oxoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide

C99	5-((2-(aminomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide
C100	N-((3-fluoro-4-methylpyridin-2-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C101	methyl 2-(4-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)acetate
C102	methyl 3-(1H-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)propanoate
C103	5-(4-(acetamidomethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C104	5-((2-(aminomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C105	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide
C106	N-(1-(5-chloro-1H-indazol-3-yl)-2-hydroxyethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C107	N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-(ureidomethyl)benzyl)nicotinamide
C108	6-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)quinoline-2-carboxamide
C109	N-((6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C110	5-(2-(aminomethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C111	methyl 3-(5-chloro-1H-indazol-3-yl)-3-(5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamido)propanoate
C112	N-((3-chloro-1H-indol-5-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide
C113	N-(2-(guanidinooxy)ethyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C114	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C115	N-((5-chloro-1H-indazol-3-yl)methyl)-5-((2-methoxyquinazolin-6-yl)methyl)nicotinamide
C116	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxooxazolidin-3-yl)benzyl)nicotinamide
C117	methyl 3-(4-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)phenyl)propanoate
C118	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-(2-oxoimidazolidin-1-yl)benzyl)nicotinamide
C119	5-(4-(3-amino-3-oxopropyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C120	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxopyrrolidin-1-yl)methyl)benzyl)nicotinamide
C121	methyl 6-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)quinoline-2-carboxylate
C122	5-(4-(2-amino-2-oxoethoxy)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C123	N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide
C124	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((N-methylacetamido)methyl)benzyl)nicotinamide

C125	(S)-5-(4-(1-acetamidoethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C126	(S)-5-(4-(1-acetamidoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide
C127	5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C128	5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C129	5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C130	5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide
C131	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)nicotinamide
C132	N-((5-chloro-1H-indazol-3-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide
C133	(R)-5-(4-(1-acetamidoethyl)benzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C134	(R)-5-(4-(1-acetamidoethyl)benzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide
C135	N-((3-chloro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)nicotinamide
C136	N-((6-(aminomethyl)pyridin-3-yl)methyl)-5-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide
C137	N-((3-chloro-1H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C138	N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C139	1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C140	1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((5-chloro-1H-indazol-3-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C141	1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-N-((6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C142	1-[6-(Acetylamino-methyl)-pyridin-3-ylmethyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
C143	1-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C144	1-[6-(Acetylamino-methyl)-pyridin-3-ylmethyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-chloro-6-fluoro-1H-indol-5-ylmethyl)-amide
C145	5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C146	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrrolidin-1-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C147	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C148	2-(5-((5-(((5-chloro-1H-indazol-3-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-1H-indol-3-yl)acetic acid
C149	2-(5-((5-(((3-chloro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-1H-indol-3-yl)acetic acid
C150	5-[6-(Acetylamino-methyl)-pyridin-3-ylmethyl]-N-(3-chloro-1H-indol-5-ylmethyl)-nicotinamide

C151	5-[6-(Acetylamino-methyl)-pyridin-3-ylmethyl]-N-(3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-nicotinamide
C152	5-[6-(Acetylamino-methyl)-pyridin-3-ylmethyl]-N-(5-chloro-1H-indazol-3-ylmethyl)-nicotinamide
C153	5-[6-(Acetylamino-methyl)-pyridin-3-ylmethyl]-N-(3-chloro-6-fluoro-1H-indol-5-ylmethyl)-nicotinamide
C154	2-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)pyridine-4-carboxamide
C155	6-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)pyrazine-2-carboxamide
C156	5-(4-(acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)pyridine-3-carboxamide
C157	1-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1,6-dihydro-6-oxopyridine-3-carboxamide
C158	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)nicotinamide
C159	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyrazin-1(2H)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide
C160	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyrrolidin-1-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide
C161	5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-indol-5-yl)methyl)nicotinamide
C162	5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)nicotinamide
C163	5-(4-(acetamidomethyl)-2,3-difluorobenzyl)-N-((5-chloro-1H-indazol-3-yl)methyl)nicotinamide
C164	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((6-(tetrahydrofuran-2-yl)pyridin-3-yl)methyl)nicotinamide
C165	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(2,3-difluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C166	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)-1,6-dihydropyridine-3-carboxamide
C167	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-3-carboxamide
C168	5-((6-(1-acetylpyrrolidin-2-yl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C169	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxoimidazolidin-1-yl)methyl)benzyl)nicotinamide
C170	1-(4-(acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C171	1-(4-(acetamidomethyl)-2,5-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C172	5-(4-(acetamidomethyl)-2,5-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C173	5-(4-(1-acetylpyrrolidin-2-yl)-3-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C174	5-(4-(1-acetylpyrrolidin-2-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C175	5-(4-(1-acetylpyrrolidin-2-yl)-2,3-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C176	5-(4-(1-acetylpyrrolidin-2-yl)-2,5-difluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide

C177	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((6-(5-oxopyrrolidin-2-yl)pyridin-3-yl)methyl)nicotinamide
C178	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide
C179	2-(4-(acetamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C180	5-(4-(acetamidomethyl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C181	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(2-fluoro-4-((2-hydroxyacetamido)methyl)benzyl)nicotinamide
C182	5-(4-((2-aminoacetamido)methyl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide 2,2,2-trifluoroacetate
C183	2-((6-(acetamidomethyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide 2,2,2-trifluoroacetate
C184	5-(4-(1-acetylpyrrolidin-2-yl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C185	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C186	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)nicotinamide
C187	5-(4-(acetamidomethyl)-5-chloro-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C188	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((6-((2-hydroxyacetamido)methyl)pyridin-3-yl)methyl)nicotinamide
C189	5-((6-((2-aminoacetamido)methyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C190	1-(4-(1-acetylpyrrolidin-2-yl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-1,6-dihydropyridine-3-carboxamide
C191	5-(4-((2-aminoacetamido)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C192	5-((4-(acetamidomethyl)-2-oxopyridin-1(2H)-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C193	5-(4-(acetamidomethyl)-3-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C194	2-(4-(acetamidomethyl)-3-methoxybenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C195	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-hydroxyacetamido)methyl)-3-methoxybenzyl)isonicotinamide
C196	2-(4-((2-aminoacetamido)methyl)-3-methoxybenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C197	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-hydroxyacetamido)methyl)benzyl)nicotinamide
C198	methyl 1-((5-(((3-chloro-6-fluoro-1H-indol-5-yl)methyl)carbamoyl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxylate
C199	5-((4-(acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)nicotinamide
C200	N-((5-chloro-1H-indazol-3-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide
C201	2-((3-(acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C202	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

C203	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-5-((4-((N-cyclopropylacetamido)methyl)-1H-pyrazol-1-yl)methyl)nicotinamide
C204	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((2-hydroxyacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide
C205	2-((6-((2-aminoacetamido)methyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C206	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide
C207	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((N-cyclopropyl-2-hydroxyacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide
C208	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide
C209	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-((N-cyclopropylacetamido)methyl)-1H-pyrazol-1-yl)methyl)isonicotinamide
C210	N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide
C211	2-((4-(acetamidomethyl)-1H-pyrazol-1-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C212	N-((5-chloro-1H-indazol-3-yl)methyl)-2-((6-((N-cyclopropylacetamido)methyl)pyridin-3-yl)methyl)isonicotinamide
C213	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(pyridin-4-yl)benzyl)isonicotinamide
C214	2-(4-(acetamidomethyl)-2-fluorobenzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C215	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((methylamino)(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)isonicotinamide
C216	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-cyclopropylbenzyl)isonicotinamide
C217	N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-(4-((N-cyclopropylacetamido)methyl)benzyl)isonicotinamide
C218	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((N-cyclopropylacetamido)methyl)benzyl)isonicotinamide
C219	2-(amino(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C220	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)isonicotinamide
C221	2-(3-(1H-pyrazol-3-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C222	2-([2,4'-bipyridin]-6-ylmethyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C223	2-(3-(1H-pyrazol-4-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C224	2-(4-(acetamidomethyl)benzyl)-N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C225	N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C226	N-((3-chloro-4-fluoro-1H-indol-5-yl)methyl)-5-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)nicotinamide
C227	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(pyridin-3-yl)benzyl)isonicotinamide
C228	2-(4-((1H-pyrazol-1-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide

C229	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(furan-2-yl)benzyl)isonicotinamide
C230	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(1-methyl-1H-pyrazol-5-yl)benzyl)isonicotinamide
C231	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(pyrimidin-5-yl)benzyl)isonicotinamide
C232	2-(3-(1H-pyrazol-1-yl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C233	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(isoxazol-4-yl)benzyl)isonicotinamide
C234	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(3,5-dimethylisoxazol-4-yl)benzyl)isonicotinamide
C235	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(hydroxymethyl)benzyl)isonicotinamide
C236	2-((6-((1H-pyrazol-1-yl)methyl)pyridin-3-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C237	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-cyano-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C238	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-fluoro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C239	2-(3-chloro-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C240	2-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C241	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((4-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C242	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3,5-dichloro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C243	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxopyrazin-1(2H)-yl)methyl)benzyl)isonicotinamide
C244	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((6-oxopyrimidin-1(6H)-yl)methyl)benzyl)isonicotinamide
C245	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(2-oxopyridin-1(2H)-yl)benzyl)isonicotinamide
C246	N-(4-((4-(((3-chloro-6-fluoro-1H-indol-5-yl)methyl)carbamoyl)pyridin-2-yl)methyl)benzyl)picolinamide
C247	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(isobutyramidomethyl)benzyl)isonicotinamide
C248	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-methylureido)methyl)benzyl)isonicotinamide
C249	2-(4-(benzamidomethyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C250	methyl 4-((4-(((3-chloro-6-fluoro-1H-indol-5-yl)methyl)carbamoyl)pyridin-2-yl)methyl)benzylcarbamate
C251	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(cyclopropanecarboxamidomethyl)benzyl)isonicotinamide
C252	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(methylsulfonamidomethyl)benzyl)isonicotinamide
C253	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-4-oxo-1-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,4-dihydropyridine-3-carboxamide
C254	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-phenoxybenzyl)isonicotinamide

C255	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-1-((3-((2-oxopyridin-1(2H)-yl)methyl)bicyclo[1.1.1]pentan-1-yl)methyl)-1H-pyrazole-4-carboxamide
C256	N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide
C257	N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C258	2-(3-carbamoyl-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)isonicotinamide
C259	2-(3-(aminomethyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C260	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-morpholinobenzyl)isonicotinamide
C261	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C262	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((1-methyl-1H-pyrazol-5-yl)methyl)benzyl)isonicotinamide
C263	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-cyclopropylureido)methyl)benzyl)isonicotinamide
C264	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyridin-3-yloxy)benzyl)isonicotinamide
C265	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((4-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C266	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C267	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide
C268	2-(4-((1H-imidazol-1-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C269	N-(4-(aminomethyl)benzyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C270	N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C271	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C272	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)picolinamide
C273	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C274	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C275	2-(4-((5-chloro-2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C276	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxo-3-(trifluoromethyl)pyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C277	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C278	2-(4-((3-chloro-2-oxopyridin-1(2H)-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C279	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide
C280	N-((6-fluoro-1H-indol-5-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

C281	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C282	N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-fluoro-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C283	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-oxo-4-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,6-dihydropyridine-2-carboxamide
C284	N-((3-chloro-1H-pyrrolo[2,3-c]pyridin-5-yl)methyl)-2-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)isonicotinamide
C285	N-((3-chloro-1H-pyrrolo[2,3-c]pyridin-5-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C286	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-chloroquinolin-3-yl)methyl)isonicotinamide
C287	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide
C288	2-([1,1'-biphenyl]-4-ylmethyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C289	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(furan-2-ylmethyl)benzyl)isonicotinamide
C290	2-(4-((1H-pyrazol-3-yl)methyl)benzyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C291	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)isonicotinamide
C292	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyridin-3-ylmethyl)benzyl)isonicotinamide
C293	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-(pyrimidin-5-ylmethyl)benzyl)isonicotinamide
C294	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(quinolin-3-ylmethyl)isonicotinamide
C295	N-((6-amino-5-chloropyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C296	N-((6-amino-5-methylpyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C297	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C298	N-((6-amino-5-methoxypyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C299	N-((3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C300	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-(4-((5-oxo-1H-1,2,4-triazol-4(5H)-yl)methyl)benzyl)isonicotinamide
C301	N-((5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C302	N-(4-bromo-2-methylbenzyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C303	N-((8-aminoquinolin-3-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C304	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide
C305	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-phenylpyridin-3-yl)methyl)isonicotinamide
C306	N-(4-bromo-3-chlorobenzyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide

C307	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-phenylthiazol-2-yl)methyl)isonicotinamide
C308	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-6-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)pyridazine-4-carboxamide
C309	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-methyl-2-(methylsulfonyl)quinolin-3-yl)methyl)isonicotinamide
C310	N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide
C311	N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide
C312	N-((6-amino-2-methylpyridin-3-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide
C313	N-(4-(aminomethyl)-3-fluorobenzyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C314	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide
C315	N-((6-amino-2-methylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C316	N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C317	N-((1-aminoisoquinolin-7-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C318	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide
C319	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide
C320	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide
C321	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C322	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide
C323	N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-fluoroquinolin-3-yl)methyl)isonicotinamide
C324	N-((1-aminoisoquinolin-6-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide
C325	N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide
C326	N-((1-aminoisoquinolin-6-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide
C327	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C328	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C329	N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C330	N-((1-aminoisoquinolin-6-yl)methyl)-2-(3-(methylsulfonyl)-4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C331	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide
C332	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((4-cyanoquinolin-6-yl)methyl)isonicotinamide

C333	N-((1-aminoisoquinolin-6-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide
C334	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((7-fluoroquinolin-3-yl)methyl)isonicotinamide
C335	N-((1-aminoisoquinolin-6-yl)methyl)-2-(4-((5-cyano-2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C336	N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide
C337	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide
C338	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-7-yl)methyl)isonicotinamide
C339	N-((1-aminoisoquinolin-6-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide
C340	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide
C341	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((7-chloroquinolin-3-yl)methyl)isonicotinamide
C342	N-((4-aminoquinazolin-7-yl)methyl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)isonicotinamide
C343	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-isocyanoquinolin-6-yl)methyl)isonicotinamide
C344	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-isocyanoquinolin-6-yl)methyl)isonicotinamide
C345	N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide
C346	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide
C347	N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide
C348	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((2-(methylsulfonyl)quinolin-6-yl)methyl)isonicotinamide
C349	N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide
C350	N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide
C351	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide
C352	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylisoquinolin-6-yl)methyl)isonicotinamide
C353	N-((1-aminoisoquinolin-6-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide
C354	2-((2-(aminomethyl)quinolin-6-yl)methyl)-N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)isonicotinamide
C355	N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-(aminomethyl)quinolin-6-yl)methyl)isonicotinamide

Table 2. Biological activity of several illustrative compounds against human plasma kallikrein

hPK	Compound No.
+++	C01, C05, C07, C08, C10, C12, C13, C14, C15, C16, C17, C18, C25, C27, C28, C29, C30, C31, C33, C38, C39, C40, C41, C42, C44, C46, C48, C49, C50, C51, C53, C54, C55, C56, C57, C60, C64, C65, C66, C68, C69, C70, C73, C77, C83, C84, C85, C89, C90, C91, C92, C93, C94, C96, C97, C103, C105, C106, C109, C114, C120, C121, C128, C129, C131, C135, C145, C150, C151, C152, C153, C154, C156, C158, C162, C163, C165, C166, C167, C168, C169, C174, C175, C176, C178, C179, C183, C184, C185, C186, C187, C188, C193, C194, C200, C202, C206, C207, C208, C210, C215, C217, C218, C219, C224, C225, C226, C228, C236, C237, C238, C239, C240, C241, C242, C243, C244, C247, C248, C250, C251, C256, C257, C258, C259, C261, C262, C263, C266, C267, C268, C270, C271, C272, C273, C274, C275, C276, C277, C278, C279, C280, C281, C282, C283, C284, C286, C287, C291, C294, C297, C299, C300, C301, C304, C308, C310, C311, C312, C314, C316, C318, C319, C320, C321, C322, C323, C324, C325, C326, C327, C328, C329, C330, C332, C333, C334, C335, C336, C337, C339, C340, C341, C343, C344, C345, C346, C349, C350, C351, C352, C355
++	C03, C04, C21, C22, C23, C24, C34, C35, C36, C37, C43, C45, C47, C59, C61, C62, C63, C71, C74, C75, C76, C78, C79, C80, C81, C82, C86, C87, C88, C95, C98, C100, C101, C107, C108, C110, C111, C112, C113, C115, C116, C117, C118, C119, C122, C123, C124, C125, C126, C127, C130, C132, C133, C134, C136, C137, C138, C139, C140, C142, C144, C146, C147, C155, C157, C159, C160, C161, C164, C170, C171, C172, C173, C177, C180, C181, C182, C189, C190, C191, C192, C195, C196, C197, C198, C203, C204, C205, C209, C212, C213, C214, C216, C220, C222, C227, C229, C231, C232, C233, C234, C245, C246, C249, C252, C253, C254, C255, C264, C265, C269, C285, C288, C289, C290, C292, C293, C296, C298, C305, C307, C309, C313, C315, C317, C331, C338, C342, C347, C348, C353, C354
+	C02, C06, C09, C11, C19, C20, C26, C32, C52, C58, C67, C72, C99, C102, C104, C141, C143, C148, C149, C199, C201, C211, C221, C223, C230, C235, C260, C295, C302, C303, C306

Example 357: The following illustrate representative pharmaceutical dosage forms, containing a compound of Formula I or II, or a pharmaceutically acceptable salt thereof ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1		mg/tablet
Compound X=	100.0	
Lactose	77.5	
Povidone		15.0
Croscarmellose sodium	12.0	
Microcrystalline cellulose		92.5
Magnesium stearate		3.0
		300.0

(ii) Tablet 2		mg/tablet
Compound X=	20.0	
Microcrystalline cellulose		410.0
Starch		50.0
Sodium starch glycolate	15.0	
Magnesium stearate		5.0
		500.0

(iii) Capsule		mg/capsule
Compound X=	10.0	
Colloidal silicon dioxide		1.5
Lactose	465.5	
Pregelatinized starch		120.0
Magnesium stearate		3.0
		600.0

(iv) Injection 1 (1 mg/ml)		mg/ml
Compound X= (free acid form)	1.0	
Dibasic sodium phosphate		12.0
Monobasic sodium phosphate		0.7
Sodium chloride		4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)		q.s.
Water for injection		q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)		mg/ml
Compound X= (free acid form)	10.0	
Monobasic sodium phosphate		0.3
Dibasic sodium phosphate		1.1
Polyethylene glycol 400	200.0	
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)		q.s.
Water for injection		q.s. ad 1 mL

(vi) Aerosol		mg/can
Compound X=	20.0	
Oleic acid		10.0
Trichloromonofluoromethane		5,000.0
Dichlorodifluoromethane		10,000.0
Dichlorotetrafluoroethane		5,000.0

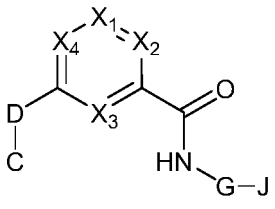
The above formulations may be prepared by conventional procedures well known in the pharmaceutical art.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

2014373735 06 Jun 2019

What is claimed is:

1. A compound of Formula IIb:



Formula IIb

wherein:

C is a bicyclic 8-12 membered heteroaryl ring selected from the group consisting of indole, quinoline, isoquinoline, and quinazoline that is optionally substituted with one or more groups independently selected from halo, cyano, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, -$(C_1\text{-}C_6)$alkyl-COOH, $-NR^aR^b$, $S(=O)_2R^e$, and $-C(=O)NR^aR^b$;

D is CH_2;

X_1 is CH and X_4 is N, or X_1 is N and X_4 is CH;

X_2 is CH;

X_3 is CH;

G is CH_2;

J is pyridine, indole, or indazole that is optionally substituted with one or more groups independently selected from halo, $(C_1\text{-}C_6)$alkyl, and $-NR^aR^b$;

each R^a is independently H or $(C_1\text{-}C_6)$alkyl;

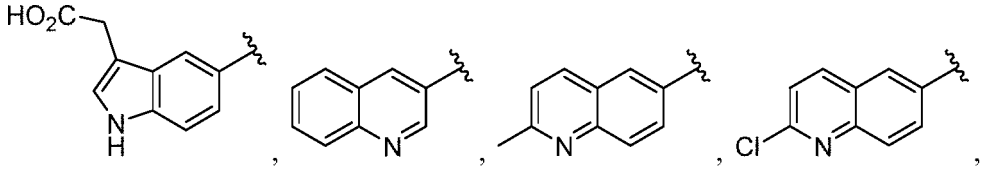
each R^b is independently H or $(C_1\text{-}C_6)$alkyl; and

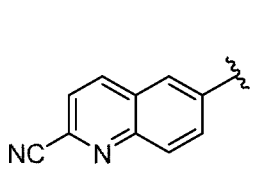
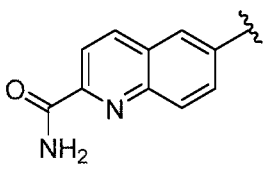
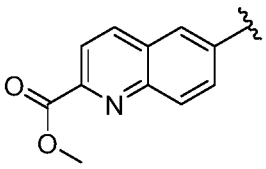
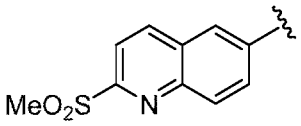
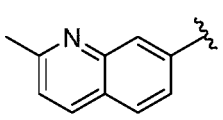
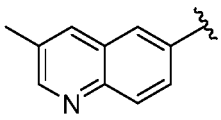
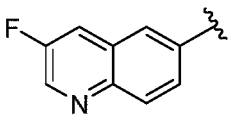
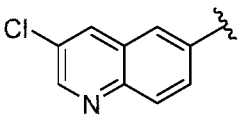
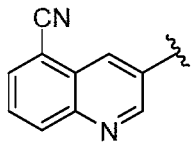
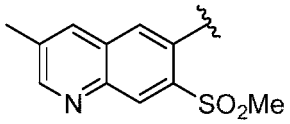
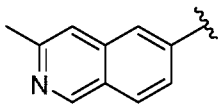
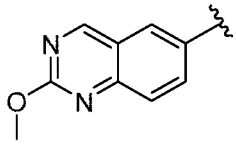
each R^e is independently H or $(C_1\text{-}C_6)$alkyl;

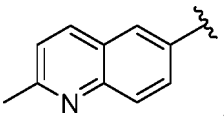
or a salt thereof.

2. The compound of claim 1, wherein C is indole, quinoline, isoquinoline, or quinazoline that is optionally substituted with one or more groups independently selected from F, Cl, CN, CH_3, OCH_3, -$CH_2C(=O)OH$, $-C(=O)OCH_3$, $-C(=O)NH_2$, and $-S(=O)_2CH_3$.

3. The compound of any one of the preceding claims, wherein C is selected from the group consisting of



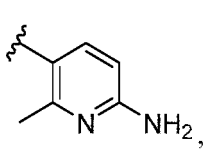
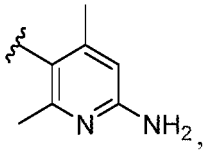
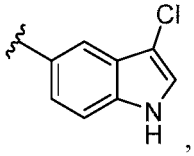
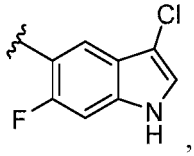
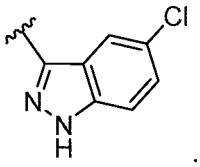
4. The compound of any one of the preceding claims, wherein C is  .

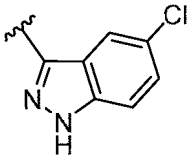
5. The compound of any one of the preceding claims, wherein X_1 is CH and X_4 is N.

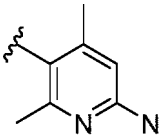
6. The compound of any one of claims 1 to 4, wherein X_1 is N and X_4 is CH.

7. The compound of any one of the preceding claims, wherein J is pyridine, indole, indazole, or isoquinoline that is optionally substituted with one or more groups independently selected from F, Cl, CH_3, and NH_2.

8. The compound of any one of the preceding claims, wherein J is selected from the group consisting of

9. The compound of any one of the preceding claims, wherein J is  .

10. The compound of any one of claims 1 to 8, wherein J is  .

2014373735 06 Jun 2019

11. A compound wherein the compound is:

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((6-methylquinolin-3-yl)methyl)isonicotinamide;

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;

N-((6-amino-2,4-dimethylpyridin-3-yl)methyl)-2-((2-methylquinolin-6-yl)methyl)isonicotinamide;

N-((1-aminoisoquinolin-6-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide; or

N-((3-chloro-6-fluoro-1H-indol-5-yl)methyl)-2-((3-methylquinolin-6-yl)methyl)isonicotinamide;

or a salt thereof.

12. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. A method of treating angioedema in a patient in need thereof comprising administering to the patient a composition of any one of the preceding claims, or a pharmaceutically acceptable salt thereof.

14. The method of claim 13, wherein the angioedema is hereditary angioedema.

15. A method of treating macular edema in a patient in need thereof comprising administering to the patient a composition of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

16. A method of treating brain edema in a patient in need thereof comprising administering to the patient a composition of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.