COLLAGEN 1 TRANSLATION INHIBITORS AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

[001] The present invention relates to a novel Collagen 1 translation inhibitors, composition and methods of preparation thereof, and uses thereof for treating Fibrosis including lung, liver, kidney, cardiac and dermal fibrosis, IPF, wound healing, scarring and gingival fibromatosis, Systemic Sclerosis, and alcoholic and non-alcoholic steatohepatitis (NASH).

BACKGROUND OF THE INVENTION

[002] The formation of fibrous connective tissue is part of the normal healing process following tissue damage due to injury or inflammation. During this process, activated immune cells including macrophages stimulate the proliferation and activation of fibroblasts, which in turn deposit connective tissue. However, abnormal or excessive production of connective tissue may lead to accumulation of fibrous material such that it interferes with the normal function of the tissue. Fibrotic growth can proliferate and invade healthy surrounding tissue, even after the original injury heals. Such abnormal formation of excessive connective tissue, occurring in a reparative or reactive process, is referred to as fibrosis.

[003] Many agents cause activation of the fibrotic process and are released in response to tissue injury, inflammation and oxidative stress. Regardless of the initiating events, a feature common to all fibrotic diseases is the conversion of tissue resident fibroblast into ECM-producing myofibroblasts that secret collagen type I. Current programs indirectly target myofibroblast activation and collagen secretion by inhibiting a single fibrosis inducing signal.

[004] Physiologically, fibrosis acts to deposit connective tissue, which can obliterate the architecture and function of the underlying organ or tissue. Defined by the pathological accumulation of extracellular matrix (ECM) proteins, fibrosis results in scarring and thickening of the affected tissue, which interferes with normal organ function. In various conditions, the formation of fibrotic tissue is characterized by the deposition of abnormally large amounts of collagen. The synthesis of collagen is also involved in a number of other pathological conditions. For example, clinical conditions and disorders associated with primary or secondary fibrosis, such as systemic sclerosis, graft-versus host disease (GVHD), pulmonary fibrosis and autoimmune disorders, are distinguished by excessive production of connective tissue, which results in the destruction of normal tissue architecture and function. These diseases can best be interpreted in terms of perturbations in cellular functions, a major manifestation of which is excessive collagen synthesis and deposition. The role of collagen in fibrosis has prompted attempts to develop drugs that inhibit its accumulation.

[005] Excessive accumulation of collagen is the major pathologic feature in a variety of clinical conditions characterized by tissue fibrosis. These conditions include localized processes, as for example, pulmonary fibrosis and liver cirrhosis, or more generalized processes, like progressive systemic sclerosis. Collagen deposition is a feature of different forms of dermal fibrosis, which in addition to

scleroderma, include localized and generalized morphea, keloids, hypertrophic scars, familial cutaneous collagenoma and connective tissue nevi of the collagen type. Recent advances in the understanding of the normal biochemistry of collagen have allowed us to define specific levels of collagen biosynthesis and degradation at which a pharmacologic intervention could lead to reduced collagen deposition in the tissues. Such compounds could potentially provide us with novel means to reduce the excessive collagen accumulation in diseases.

[006] Fibrosis of the liver, also referred to herein as hepatic fibrosis, may be caused by various types of chronic liver injury, especially if an inflammatory component is involved. Self-limited, acute liver injury (e.g., acute viral hepatitis A), even when fulminant, does not necessarily distort the scaffolding architecture and hence does not typically cause fibrosis, despite loss of hepatocytes. However, factors such as chronic alcoholism, malnutrition, hemochromatosis, and exposure to poisons, toxins or drugs, may lead to chronic liver injury and hepatic fibrosis due to exposure to hepatotoxic chemical substances. Hepatic scarring, caused by surgery or other forms of injury associated with mechanical biliary obstruction, may also result in liver fibrosis.

[007] Fibrosis itself is not necessarily symptomatic, however it can lead to the development of portal hypertension, in which scarring distorts blood flow through the liver, or cirrhosis, in which scarring results in disruption of normal hepatic architecture and liver dysfunction. The extent of each of these pathologies determines the clinical manifestation of hepato-fibrotic disorders. For example, congenital hepatic fibrosis affects portal vein branches, largely sparing the parenchyma. The result is portal hypertension with sparing of hepatocellular function.

Treatment

[008] Attempts to develop anti-fibrotic agents for the treatment of various disorders have been reported. However, treatment of established fibrosis, formed after months or years of chronic or repeated injury, still remains a challenge.

[009] Treatments aimed at reversing the fibrosis are usually too toxic for long-term use (e.g. corticosteroids, penicillamine) or have no proven efficacy (e.g. colchicine).

[0010] Many patients do not respond to available treatments for fibrotic disorders, and long-term treatment is limited by toxicity and side effects. Therefore, a need remains for developing therapeutic modalities aimed at reducing fibrosis. The development of safe and effective treatments for established cirrhosis and portal hypertension and for attenuating fibrosis would be highly beneficial.

[0011] Attempts to treat idiopathic pulmonary fibrosis (IPF) with a combination of anti-inflammatory drugs (prednisone, azathioprine and N-acetyl-l-cysteine (NAC)), failed to improve outcomes, and instead increased mortality. In 2014, two drugs, pirfenidone, a drug with poorly understood mechanisms, and nintedanib, a tyrosine kinase inhibitor, were approved for the treatment of IPF mainly on the basis of their ability to reduce the decrease in forced vital capacity (FVC) and to slow the pace of disease progression. To date, however, it is unclear whether these drugs improve symptoms such as dyspnoea and cough, or whether their beneficial effect on functional decline translates to increased survival.

[0012] The compounds of this invention target activated fibroblasts and collagen over production and can therefore be used for treating fibrosis, including primary or secondary fibrosis, such as systemic sclerosis, graft-versus host disease (GVHD), pulmonary fibrosis and autoimmune disorders, lung fibrosis and idiopathic pulmonary fibrosis (IPF), as well as localized processes, as for example, pulmonary fibrosis and liver cirrhosis, or more generalized processes, like progressive systemic sclerosis. The compounds can be further useful in the treatment of different forms of dermal fibrosis, which in addition to scleroderma, include localized and generalized morphea, keloids, hypertrophic scars, familial cutaneous collagenoma and connective tissue nevi of the collagen type. The compounds can be further useful in the treatment of lung fibrosis and idiopathic pulmonary fibrosis (IPF), as well as hepatic fibrosis, resulting from hepatic scarring, caused by surgery or other forms of injury associated with mechanical biliary obstruction. Such fibrosis can lead to portal hypertension, in which scarring distorts blood flow through the liver, or cirrhosis as well as other hepato-fibrotic disorders including Non-alcoholic steatohepatitis (NASH), and alcoholic steatohepatitis (ASH), non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD), which can similarly be treated by compounds of the invention.

SUMMARY OF THE INVENTION

[0013] This invention provides a compound or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below. In various embodiments, the compound is a Collagen I translation inhibitor.

[0014] This invention provides a compound or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of Compound **100**.

[0015] This invention provides a compound or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of Compound **118**.

[0016] This invention further provides a pharmaceutical composition comprising a compound or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variants (e.g., deuterated analog), PROTAC, pharmaceutical product or any combination thereof, represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, and a pharmaceutically acceptable carrier.

[0017] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting fibrosis in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein

below, to a subject suffering from fibrosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit fibrosis in said subject. In some embodiments, the fibrosis is a systemic fibrotic disease. In some embodiments, the systemic fibrotic disease is systemic sclerosis, multifocal fibrosclerosis (IgG4-associated fibrosis), nephrogenic systemic fibrosis, sclerodermatous graft vs. host disease, or any combination thereof. In some embodiments, the fibrosis is an organ-specific fibrotic disease. In some embodiments, the organ-specific fibrotic disease is lung fibrosis, cardiac fibrosis, kidney fibrosis, pulmonary fibrosis, liver and portal vein fibrosis, radiation-induced fibrosis, bladder fibrosis, intestinal fibrosis, peritoneal sclerosis, diffuse fasciitis, wound healing, scaring, or any combination thereof. In some embodiments, the lung fibrosis is idiopathic pulmonary fibrosis (IPF). In some embodiments, the cardiac fibrosis is hypertension-associated cardiac fibrosis, Post-myocardial infarction, Chagas disease-induced myocardial fibrosis or any combination thereof. In some embodiments, the kidney fibrosis is diabetic and hypertensive nephropathy, urinary tract obstruction-induced kidney fibrosis, inflammatory/autoimmune-induced kidney fibrosis, aristolochic acid nephropathy, polycystic kidney disease, or any combination thereof. In some embodiments, the pulmonary fibrosis is idiopathic pulmonary fibrosis, silica-induced pneumoconiosis (silicosis), asbestos-induced pulmonary fibrosis (asbestosis), chemotherapeutic agent-induced pulmonary fibrosis, or any combination thereof. In some embodiments, the liver and portal vein fibrosis is alcoholic and nonalcoholic liver fibrosis, hepatitis C-induced liver fibrosis, primary biliary cirrhosis, parasite-induced liver fibrosis (schistosomiasis), or any combination thereof. In some embodiments, the diffuse fasciitis is localized scleroderma, keloids, dupuytren's disease, peyronie's disease, myelofibrosis, oral submucous fibrosis, or any combination thereof. In some embodiments, the fibrosis is primary or secondary fibrosis. In some embodiments, the fibrosis is a result of systemic sclerosis, graft-versus host disease (GVHD), pulmonary fibrosis, autoimmune disorder, tissue injury, inflammation, oxidative stress or any combination thereof. In some embodiments, the fibrosis is hepatic fibrosis, lung fibrosis or dermal fibrosis. In some embodiments, the subject has liver cirrhosis. In some embodiments, the dermal fibrosis is scleroderma. In some embodiments, the dermal fibrosis is a result of a localized or generalized morphea, keloids, hypertrophic scars, familial cutaneous collagenoma, connective tissue nevi of the collagen type, or any combination thereof. In some embodiments, hepatic fibrosis is a result of hepatic scarring or chronic liver injury. In some embodiments, the chronic liver injury results from alcoholism, malnutrition, hemochromatosis, exposure to poisons, toxins or drugs.

[0018] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting lung fibrosis in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from lung fibrosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit lung fibrosis in said subject. In some embodiments, the lung fibrosis is idiopathic pulmonary fibrosis (IPF).

[0019] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting idiopathic pulmonary fibrosis (IPF) in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in

Table 1, as defined herein below, to a subject suffering from idiopathic pulmonary fibrosis (IPF) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit idiopathic pulmonary fibrosis (IPF) in said subject.

[0020] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting hepato-fibrotic disorder in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from hepato-fibrotic disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit hepato-fibrotic disorder in said subject. In some embodiments, the hepato-fibrotic disorder is a portal hypertension, cirrhosis, congenital hepatic fibrosis or any combination thereof.

[0021] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cirrhosis in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from cirrhosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit cirrhosis in said subject. In some embodiments, the cirrhosis is a result of hepatitis or alcoholism.

[0022] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic steatohepatitis (ASH) in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from alcoholic steatohepatitis (ASH) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the alcoholic steatohepatitis (ASH) in said subject.

[0023] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a non-alcoholic steatohepatitis (NASH) in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from non-alcoholic steatohepatitis (NASH) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the non-alcoholic steatohepatitis (NASH) in said subject.

[0024] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an alcoholic fatty liver disease (AFLD) in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from alcoholic fatty liver disease (AFLD) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the alcoholic fatty liver disease (AFLD) in said subject.

[0025] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a non alcoholic fatty liver disease (NAFLD) in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from non alcoholic fatty liver disease

(NAFLD) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the non alcoholic fatty liver disease (NAFLD) in said subject.

[0026] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from an autoimmune disease or disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the autoimmune disease or disorder in said subject.

[0027] This invention further provides amethod of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject, comprising administering a compound represented by the structure of formula **I-V**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from an autoimmune disease or disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the autoimmune disease or disorder in said subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

[0029] **Figure 1** demonstrates the effect of Compound **100** on expression of Collagen 1 in WI38 Human Lung Fibroblasts cells. WI-38 cells were plated in 384-well plate and activated with fibroblast activation cocktail for 72 hours and treated with compounds in the last 48 hours. Compound **100** was tested at the indicated concentrations (0.005, 0.014, 0.12, 0.37, 1, 3, and 10 mM). Collagen 1 levels were determined by immunofluorescence microscopy using an anti-collagen 1 antibody. Relative expression of collagen was determined and normalized to control cells treated with DMSO. Normalized collagen expression is presented on the Y-axis. The EC_{50} of Compound **100** is 163 nM.

[0030] **Figure 2** depicts the short-term stability of Nanosuspension of Compound **100** as observed by the dynamic light scattering Z-potential of size particles.

[0031] **Figure 3** depicts the short-term stability of Nanosuspension of Compound **100** as observed by HPLC assay, measuring the sample purity over time. Nanosuspension of Compound **100** appear to be chemically and physically stable for up to 6 weeks at both the storage condition. Increase of the dissolved fraction observed from t=3 days in both storage conditions. * Standard purity at 254 nm is 99.33%.

[0032] **Figure 4A-B** depict the XRPD of Nanosuspension of Compound **100** at 25^0c (**Figure 4A**) and at 2-8^0c (**Figure 4B**). No change in the physical form of the compound was noticed after 6 weeks at both storage conditions.

[0033] **Figure 5** depicts Compound **100** single-dose pharmacokinetics study in Balb/C mice. PK profile of Compound **100**, IV at 10mg/kg (triangles), PO at 3 (circle with solid line), 10 (circle with large hatched line) and 30 mg/kg (circle with small hatch line).

[0034] **Figure 6** depicts a multi-dose 5-day PK Study (Day 1 and 5) of Compound **100** in Balb/C mice. PK profile: IV at 10mg/kg, PO at 3, 10, 30 and 100mg/kg (as indicated to the right of the graph). IV dosing of Compound **100** shows low clearance (11% LBF, assuming mouse LBF of 120 mL/min/kg) with a half-life of 1.9 h; and moderate volume of distribution at 1.5 L/Kg. PO Multi-dose PK study was carried out as BID for 5 days, with plasma collection on day 1 and 5 only, but administration of drug was at zero hour and eighth hour daily. Nanosuspension formulation was used and prepared fresh for each day of the administration.

[0035] **Figure 7** depicts the IV administration single-dose PK study comparison between Compound **100** and **Compound A**. PK graph administration: IV at 10mg/kg of **Compound 100** and **Compound A**. IV administration of **Compound 100** and **Compound A** showed similar levels of exposure of the two compounds, with lower observed clearance value for **Compound 100**.

[0036] **Figure 8** depicts the PO administration single-dose PK study comparison between **Compound 100** and **Compound A**. Both **Compound 100** and **Compound A** were administrated as PO at 3, 10, 30mg/kg. **Compound 100** showed a steady PO bioavailability at all three dosing levels. In contrast, **Compound A** showed an increased bioavailability from 32.3% to 273%, as the dosing level increased from 3 to 100 mg/kg. This phenomenon may relate to saturation of efflux transported by **Compound A** during the absorption phase.

[0037] **Figure 9** depicts the study schedule.

[0038] **Figure 10** depicts the H&E staining of lung tissue sections. **G1** (Group 1) was treated with saline solution and not Bleomycin; **G2** (Group 2) was treated with Bleomycin 0.66mg/kg; **G3** (Group 3) was treated with Bleomycin 0.66mg/kg followed by administration of Compound **100** at 10mg/kg; **G4** (Group 4) was treated with Bleomycin 0.66mg/kg followed by administration of Compound **100** at 30mg/mg; **G5** (Group 5) was treated with Bleomycin 0.66mg/kg followed by administration of Nintedanib 60 mg/kg; Arrows point to fibrotic tissues in lung slices. Images are of two different mice for each group.

[0039] **Figure 11** depicts the Quantification Morphometry of H&E Staining. Statistical significance was calculated using Mann-Whitney one-tailed test.

[0040] **Figure 12** depicts the Masson-Trichrome staining of lung sections. **G1** was (Group 1) was treated with saline solution and not Bleomycin; **G2** (Group 2) was treated with Bleomycin 0.66mg/kg; **G3** (Group 3) was treated with Bleomycin 0.66mg/kg followed by administration of Compound **100** at 10 mg/mg; **G4** (Group 4) was treated with Bleomycin 0.66mg/kg followed by administration of Compound **100** at 30 mg/kg; **G5** (Group 5) was treated with Bleomycin 0.66mg/kg followed by administration of Nintedanib 60 mg/kg; **G3** and **G4** showed an increasing reduction for fibrotic tissue compared to **G2**. **G4** had less fibrotic areas than Nintendanib (the leading treatment for fibrosis approved in the market). Arrows point to fibrotic tissues in lung slices. Images are of two different mice for each group.

[0041] **Figure 13** depicts a quantification morphometry of Masson Trichome Staining. Statistical significance was calculated using Mann-Whitney one-tailed test.

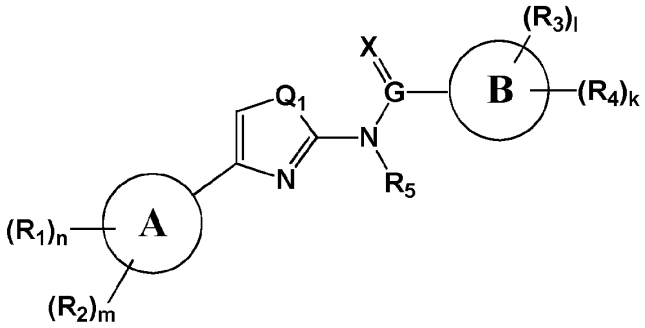
[0042] **Figure 14** depicts the Modified Ashcroft score in Belomycin induced lung fibrosis. Statistical significance was calculated using Mann-Whitney one-tailed test relative to model vehicle control. ***, p=0.0001, ****, p<0.0001

[0043] **Figure 15** depicts a Cytotoxicity window of Compound **102** of this invention and *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide* (Compound **B**).

[0044] **Figures 16A-B** depict the kinetic solubility at pH 7.4 (**Figure 16A**) and hERG channel inhibition (**Figure 16B**) of Compounds **102** of this invention compared to Compound **B**.

DETAILED DESCRIPTION OF THE INVENTION

[0045] In various embodiments, this invention is directed to a compound represented by the structure of formula **I**:



I

wherein

A and **B** rings are each independently a single or fused aromatic or heteroaromatic ring system (e.g., **A:** phenyl, thiophene, imidazole, pyrazole, pyrimidine, 2-, 3- or 4-pyridine, benzimidazole, indole, benzothiazole, benzooxazole, imidazopyridin, pyrazolopyridine, pyrrolopyridine, pyridazine, or pyrazine; **B**: phenyl, pyrimidine, 2-, 3- or 4-pyridine, pyridazine or pyrazine, thiophene, thiazole, pyrrole, imidazole, indazole), or a single or fused C_3-C_{10} cycloalkyl (e.g. **A**: pyrrolidin-2-one; **B**: bicyclo[1.1.1]pentyl, cyclobutyl, cyclohexyl, cyclopentyl,) or a single or fused C_3-C_{10} heterocyclic ring (e.g., morpholine, piperidine, piperazine, tetrahydro-2H-pyran, azetidine, pyrrolidin-2-one);

$\mathbf{R_1}$ and $\mathbf{R_2}$ are each independently H, F, Cl, Br, I, OH, SH, R_8-OH (e.g. CH_2OH), R_8-SH, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3, CH_2-O-CH_2-CH_2-O-CH_3, CH_2-O-CH_3), -O-R_8-O-R_{10} (e.g., O-CH_2-CH_2-O-CH_3), -R_8-O-R_6-R_{30} (e.g., CH_2O-tetrahydro-*2H*-pyrane, CH_2O-CH_2-CCH, CH_2O-CH_2CH_2O-CH_3, CH_2-O-CH_2CH_2NH-CH_3, CH_2O-CH_2CH_2S-CH_3, CH_2O-$CH_2CH_2S(O)CH_3$, CH_2O-$CH_2CH_2SO_2$-CH_3, CH_2O-CH_2CF_2H, CH_2-O-CH_2-CH_2-O-CH_3, CH_2O-CH_2-C(H)(OH)-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH-CH_3, CH_2-NH-C(O)CH_3, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R (e.g., NHCO-Ph, NHCO-CH_3) , NHC(O)-R_{10} (e.g., NHCO-CH_3),

$NHCO\text{-}N(R_{10})(R_{11})$, COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$, $R_8\text{-}C(O)\text{-}R_{10}$, C(O)H, $C(O)\text{-}R_{10}$, $C_1\text{-}C_5$ linear or branched C(O)-haloalkyl, $-C(O)NH_2$, C(O)NHR (e.g., C(O)NH-Ph), $C(O)N(R_{10})(R_{11})$, SO_2R, $SO_2N(R_{10})(R_{11})$, $NHSO_2(R_{10})$ (e.g., $NHSO_2CH_3$), $CH(CF_3)(NH\text{-}R_{10})$, $C_1\text{-}C_5$ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), $C_2\text{-}C_5$ linear or branched, substituted or unsubstituted alkenyl, $C_1\text{-}C_5$ linear, branched or cyclic haloalkyl (e.g., CHF_2), $C_1\text{-}C_5$ linear, branched or cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, $C_1\text{-}C_5$ linear or branched thioalkoxy, $C_1\text{-}C_5$ linear or branched haloalkoxy, $C_1\text{-}C_5$ linear or branched alkoxyalkyl, substituted or unsubstituted $C_3\text{-}C_8$ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., azetidine, pyridine), substituted or unsubstituted aryl (e.g., phenyl) or substituted or unsubstituted benzyl;

or $\mathbf{R_2}$ and $\mathbf{R_1}$ are joined together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., 1,4-dioxane, 2,3-dihydro-1,4-dioxine, dioxol, dioxolpyridine) ring;

$\mathbf{R_3}$ and $\mathbf{R_4}$ are each independently H, F, Cl, Br, I, OH, SH, $R_8\text{-}OH$, $R_8\text{-}SH$, $-R_8\text{-}O\text{-}R_{10}$ (e.g., $CH_2\text{-}CH_2\text{-}O\text{-}CH_3$, $CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_3$), $R_8\text{-}(C_3\text{-}C_8$ cycloalkyl), $R_8\text{-}$(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, $-CH_2CN$, $-R_8CN$, NH_2, NHR, $N(R)_2$, $N(R_{10})(R_{11})$ (e.g., morpholine, piperazine, 1- or 4-(methylsulfonyl)piperazine, 1-(piperazin-1-yl)ethanone), $R_8\text{-}N(R_{10})(R_{11})$, $R_9\text{-}R_8\text{-}N(R_{10})(R_{11})$, $B(OH)_2$, $-OC(O)CF_3$, $-OCH_2Ph$, $NHC(O)\text{-}R_{10}$, $NHCO\text{-}N(R_{10})(R_{11})$, COOH, -C(O)Ph, $C(O)O\text{-}R_{10}$, $R_8\text{-}C(O)\text{-}R_{10}$, C(O)H, $C(O)\text{-}R_{10}$, $C_1\text{-}C_5$ linear or branched C(O)-haloalkyl, $-C(O)NH_2$, C(O)NHR (e.g., $C(O)NH(CH_3)_2O\text{-}CH_3$), $C(O)N(R_{10})(R_{11})$ (e.g., C(O)-piperidine, C(O)-pyrrolidine, $C(O)N(CH_3)_2$, C(O)-piperazine), SO_2R, $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH\text{-}R_{10})$, $C_1\text{-}C_5$ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), $C_2\text{-}C_5$ linear or branched, substituted or unsubstituted alkenyl, $C_1\text{-}C_5$ linear, branched or cyclic haloalkyl (e.g., CHF_2), $C_1\text{-}C_5$ linear, branched or cyclic alkoxy (e.g. methoxy, 1-(methylsulfonyl)piperidin-4-oxy, 1-(methyl)piperidin-4-oxy, 1-(ethanone)piperidin-4-oxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, $C_1\text{-}C_5$ linear or branched thioalkoxy, $C_1\text{-}C_5$ linear or branched haloalkoxy, $C_1\text{-}C_5$ linear or branched alkoxyalkyl, substituted or unsubstituted $C_3\text{-}C_8$ cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted, single, spirocyclic, fused, or bridged $C_3\text{-}C_{10}$ heterocyclic ring (e.g., piperazine, 1-(2-methoxyethyl)piperazine, 1-, or 4-methylpiperazine, 1- or 4-(methylsulfonyl)piperazine, 1- or 4-(methylsulfonyl)piperidine, 2-methoxy-1-(piperazin-1-yl)ethenone, 1-(piperazin-1-yl)ethanone, 2-(dimethylamino)-1-(piperazin-1-yl)ethanone, 2-(dimethylamino)-1-(piperazin-1-yl)propanone, 2-hydroxy-1-(piperazin-1-yl)ethenone, *N*-methylpiperazine-1-carboxamide piperidin-4-ol, piperidin-3-ol, morpholine, 3-methylmorpholine, 3-hydroxypiperidine, tetrahydro-*2H*-pyrane, tetrahydro-2H-thiopyran 1,1-dioxide, pyrazole, thiazole, imidazole, pyrrolidine, pyrrolidinone, octahydropyrrolo[1,2-α]pyrazine, 6-methyl-2,6-diazaspiro[3.3]heptane, 2-oxa-7-azaspiro[3.5]nonane, 1-(2,6-diazaspiro[3.3]heptan-2-yl)ethenone, 2-methoxy-1-(2,6-diazaspiro[3.3]heptan-2-yl)ethenone, 2,8-diazaspiro[4.5]decan-1-one, 2-oxa-7-azaspiro[3.5]nonane), substituted or unsubstituted aryl (e.g., phenyl) or substituted or unsubstituted benzyl;

or R_3 and R_4 are joined together to form a 5 or 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring;

R_5 is H, R_{20}, F, Cl, Br, I, OH, SH, R_8-OH, R_8-SH, -R_8-O-R_{10}, R_8-(C_3-C_8 cycloalkyl), R_8-(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$, R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, $NHC(O)$-R_{10}, $NHCO$-$N(R_{10})(R_{11})$, COOH, -C(O)Ph, $C(O)O$-R_{10}, R_8-$C(O)$-R_{10}, C(O)H, $C(O)$-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$, SO_2R, $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH$-$R_{10})$, C_2-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), C_1-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 3-8 membered heterocyclic ring, substituted or unsubstituted aryl, or substituted or unsubstituted benzyl;

R_6 is $[CH_2]_w$

wherein **w** is between 0 and 10 (e.g., 0, 1, 2);

R_8 is $[CH_2]_p$

wherein **p** is between 1 and 10 (e.g., 1);

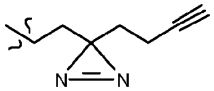
R_9 is $[CH]_q$, $[C]_q$

wherein **q** is between 2 and 10;

R_{10} and R_{11} are each independently H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., 1-(methylsulfonyl)piperidine, 1-(methylsulfonyl)piperazine, tetrahydro-*2H*-pyrane, morpholine, thiomorpholine 1,1-dioxide, methyl-pyrrolidine, methyl-piperidine), C(O)-alkyl, or $S(O)_2$-alkyl;

or R_{10} and R_{11} are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, piperazine, piperidine, pyrrolidine, 1-methylpyrrolidin-2-one, oxetane, azetidine, 1-methylazetidine, 1-(piperazin-1-yl)ethanone);

R_{20} is represented by the following structure:



R_{30} is H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, C(H)(OH)(CH_3), methyl, ethyl, CH_2-CH_2-O-CH_3), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), C_1-C_5 linear or branched thioalkoxy (e.g., S-CH_3), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane), $N(R_{10})(R_{11})$ (e.g., N(H)(CH_3), S(O)R (e.g., S(O)-CH_3), SO_2R (e.g., SO_2-CH_3), or C(O)R;

Q_1 is NH, S, or O;

G=X is C=O, C=S, S=O or SO_2;

R is H, OH, F, Cl, Br, I, CN, CF_3, NO_2, NH_2, $NH(R_{10})$ (e.g., $NH(CH_3)$), $N(R_{10})(R_{11})$, R_{20}, C_1-C_5 linear or branched, C_1-C_5 substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH_2CH_2OH, $CH_2CH_2OCH_3$), R_8-R_{10} (e.g., CH_2-OH, CH_2CH_2-OH), C(O)-R_{10} (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine, C(O)-CH_3), C_1-C_5 substituted or unsubstituted C(O)-alkyl (e.g., C(O)-CH_2CH_2-OCH_3, C(O)-CH_3, C(O)-CH_2-$N(CH_3)_2$, C(O)-CH_2-CH_2-$N(CH_3)_2$, C(O)-CH_2-OH), C(O)-R_8-R_{10} (e.g., C(O)-CH_2CH_2-OH), C(O)-substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine), C_1-C_5 substituted or unsubstituted SO_2-alkyl (e.g., SO_2-CH_3), C_1-C_5 substituted or unsubstituted C(O)-NH-alkyl (e.g., C(O)-NH-CH_3), C_1-C_5 linear or branched C(O)-O-alkyl (e.g., C(O)-O-tBu), C_1-C_5 linear or branched alkoxy, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine); or

two geminal **R** substitutions are joined together to form a 3 - 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopropyl, cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring;

n and **l** are each independently an integer between 1 and 3 (e.g., 1 or 2);

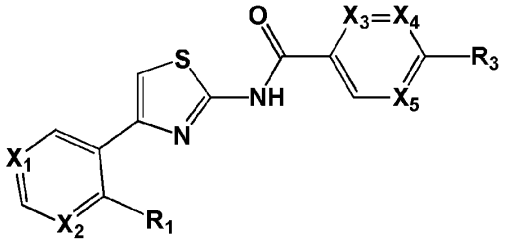
m and **k** are each independently an integer between 0 and 3 (e.g., 0, 1);

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, reverse amide, pharmaceutical product or any combination thereof.

[0046] In various embodiments, non limiting examples of the substitution included by the term "substituted" as defined herein include: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., C(O)-CH_3, C(O)-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), amide (e.g., C(O)-NH-alkyl or NH-C(O)-alkyl), C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, NH_2, N(H)(R), $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl or any combination thereof. In some embodiments, the term "substituted" according to this invention refers to at least one group selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, tertbutyl, pentyl, isopentyl, neopentyl, hexyl), C_1-C_5 linear or branched alkoxy (e.g. OCH_3), C_2-C_5 linear or branched alkynyl (e.g. CCH), C_1-C_5 linear or branched thioalkoxy (e.g. SCH_3), C_1-C_5 linear or branched alkylsulfinyl (e.g. S(O)CH_3), C_1-C_5 linear or branched alkylsulfonyl (e.g. $S(O)_2$-CH_3), NH_2, C_1-C_5 linear or branched N(H)(alkyl) (e.g., N(H)(CH_3)), and C_1-C_5 linear or branched $N(alkyl)_2$; each represents a separate embodiment according to this invention. In some embodiments, substitutions include at least one group selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, C_1-C_5 linear or branched alkoxy (e.g. OCH_3), C_2-C_5 linear

or branched alkynyl (e.g. CCH), C_1-C_5 linear or branched thioalkoxy (e.g. SCH_3), C_1-C_5 linear or branched alkylsulfinyl (e.g. $S(O)CH_3$), C_1-C_5 linear or branched alkylsulfonyl (e.g. $S(O)_2$-CH_3), C_1-C_5 linear or branched N(H)(alkyl) (e.g., $N(H)(CH_3)$) and C_1-C_5 linear or branched $N(alkyl)_2$; each represents a separate embodiment according to this invention.

[0047] In various embodiments, this invention is directed to a compound represented by the structure of formula **II**:



II

wherein

R_1 is H, F, Cl, Br, I, OH, SH, R_8-OH (e.g. CH_2OH), R_8-SH, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3, CH_2-O-CH_2-CH_2-O-CH_3, CH_2-O-CH_3), -O-R_8-O-R_{10} (e.g., O-CH_2-CH_2-O-CH_3), -R_8-O-R_6-R_{30} (e.g., CH_2O-tetrahydro-*2H*-pyrane, CH_2O-CH_2-CCH, CH_2O-CH_2CH_2O-CH_3, CH_2O-CH_2CH_2NH-CH_3, CH_2-O-CH_2CH_2S-CH_3, CH_2O-$CH_2CH_2S(O)CH_3$, CH_2O-$CH_2CH_2SO_2$-CH_3, CH_2O-CH_2CF_2H, CH_2-O-CH_2-CH_2-O-CH_3, CH_2O-CH_2-C(H)(OH)-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH-CH_3, CH_2-NH-C(O)CH_3, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R (e.g., NHCO-Ph, NHCO-CH_3) , NHC(O)-R_{10} (e.g., NHCO-CH_3), NHCO-$N(R_{10})(R_{11})$, COOH, -C(O)Ph, C(O)O-R_{10}, R_8-C(O)-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -$C(O)NH_2$, C(O)NHR (e.g., C(O)NH-Ph), $C(O)N(R_{10})(R_{11})$, SO_2R, $SO_2N(R_{10})(R_{11})$, $NHSO_2(R_{10})$ (e.g., $NHSO_2CH_3$), $CH(CF_3)$(NH-R_{10}), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., azetidine, pyridine), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted benzyl;

R_3 is H, F, Cl, Br, I, OH, SH, R_8-OH, R_8-SH, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3, CH_2-O-CH_2-CH_2-O-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, $N(R_{10})(R_{11})$ (e.g., morpholine, piperazine, 1-(piperazin-1-yl)ethenone, 1- or 4-(methylsulfonyl)piperazine), R_8-$N(R_{10})(R_{11})$, R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R_{10}, NHCO-$N(R_{10})(R_{11})$, COOH, -C(O)Ph, C(O)O-R_{10}, R_8-C(O)-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -$C(O)NH_2$, C(O)NHR (e.g.,

$C(O)NH(CH_3)_2O\text{-}CH_3$), $C(O)N(R_{10})(R_{11})$ (e.g., C(O)-piperidine, C(O)-pyrrolidine, $C(O)N(CH_3)_2$, C(O)-piperazine), SO_2R, $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH\text{-}R_{10})$, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, 1-(methylsulfonyl)piperidin-4-oxy, 1-(methyl)piperidin-4-oxy, 1-(ethanone)piperidin-4-oxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted, single, spirocyclic, fused, or bridged C_3-C_{10} heterocyclic ring (e.g., piperazine, 1-(2-methoxyethyl)piperazine, 1-, or 4-methylpiperazine, 1- or 4-(methylsulfonyl)piperazine, 1- or 4-(methylsulfonyl)piperidine, 2-methoxy-1-(piperazin-1-yl)ethenone, , 1-(piperazin-1-yl)ethanone, 2-(dimethylamino)-1-(piperazin-1-yl)ethanone, 2-(dimethylamino)-1-(piperazin-1-yl)propanone, 2-hydroxy-1-(piperazin-1-yl)ethenone, *N*-methylpiperazine-1-carboxamide piperidin-4-ol, piperidin-3-ol, morpholine, 3-methylmorpholine, 3-hydroxypiperidine, tetrahydro-*2H*-pyrane, tetrahydro-2H-thiopyran 1,1-dioxide, pyrazole, thiazole, imidazole, pyrrolidine, pyrrolidinone, octahydropyrrolo[1,2-α]pyrazine, 6-methyl-2,6-diazaspiro[3.3]heptane, 2-oxa-7-azaspiro[3.5]nonane, 1-(2,6-diazaspiro[3.3]heptan-2-yl)ethenone, 2-methoxy-1-(2,6-diazaspiro[3.3]heptan-2-yl)ethenone, 2,8-diazaspiro[4.5]decan-1-one, 2-oxa-7-azaspiro[3.5]nonane), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted benzyl;

$\mathbf{X_1}$, $\mathbf{X_2}$ $\mathbf{X_3}$, $\mathbf{X_4}$ and $\mathbf{X_5}$ are each indepednetly C or N;

$\mathbf{R_6}$ is $[\mathbf{CH_2}]_w$

wherein **w** is between 0 and 10 (e.g., 0, 1, 2);

$\mathbf{R_8}$ is $[\mathbf{CH_2}]_p$

wherein **p** is between 1 and 10 (e.g., 2);

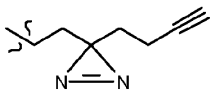
$\mathbf{R_9}$ is $[CH]_q$, $[C]_q$

wherein **q** is between 2 and 10;

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independently H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, $CH_2\text{-}CH_2\text{-}O\text{-}CH_3$), C_1-C_5 linear or branched alkoxy (e.g., $O\text{-}CH_3$), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., 1-(methylsulfonyl)piperidine, 1-(methylsulfonyl)piperazine, tetrahydro-*2H*-pyrane, morpholine, thiomorpholine 1,1-dioxide, methyl-pyrrolidine, methyl-piperidine), C(O)-alkyl, or $S(O)_2$-alkyl;

or $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, piperazine, piperidine, pyrrolidine, 1-methylpyrrolidin-2-one , oxetane, azetidine, 1-methylazetidine, 1-(piperazin-1-yl)ethanone),

$\mathbf{R_{20}}$ is represented by the following structure:



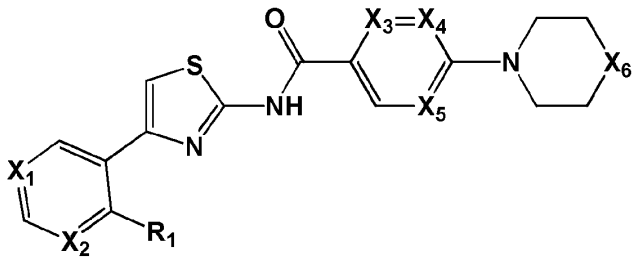
R_{30} is H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, C(H)(OH)(CH_3), methyl, ethyl, CH_2-CH_2-O-CH_3), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), C_1-C_5 linear or branched thioalkoxy (e.g., S-CH_3), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane), N(R_{10})(R_{11}) (e.g., N(H)(CH_3), S(O)R (e.g., S(O)-CH_3), SO_2R (e.g., SO_2-CH_3), or C(O)R;

R is H, OH, F, Cl, Br, I, CN, CF_3, NO_2, NH_2, NH(R_{10}) (e.g., NH(CH_3)), N(R_{10})(R_{11}), R_{20}, C_1-C_5 linear or branched, C_1-C_5 substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH_2CH_2OH, $CH_2CH_2OCH_3$), R_8-R_{10} (e.g., CH_2-OH, CH_2CH_2-OH), C(O)-R_{10} (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine, C(O)-CH_3), C_1-C_5 substituted or unsubstituted C(O)-alkyl (e.g., C(O)-CH_2CH_2-OCH_3, C(O)-CH_3, C(O)-CH_2-N(CH_3)$_2$, C(O)-CH_2-CH_2-N(CH_3)$_2$, C(O)-CH_2-OH), C(O)-R_8-R_{10} (e.g., C(O)-CH_2CH_2-OH), C(O)-substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine), C_1-C_5 substituted or unsubstituted SO_2-alkyl (e.g., SO_2-CH_3), C_1-C_5 substituted or unsubstituted C(O)-NH-alkyl (e.g., C(O)-NH-CH_3), C_1-C_5 linear or branched C(O)-O-alkyl (e.g., C(O)-O-tBu), C_1-C_5 linear or branched alkoxy, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine); or

two geminal **R** substitutions are joined together to form a 3 - 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopropyl, cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring;

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, reverse amide, pharmaceutical product or any combination thereof.

[0048] In various embodiments, this invention is directed to a compound represented by the structure of formula **III**:



III

wherein

R_1 is H, F, Cl, Br, I, OH, SH, R_8-OH (e.g. CH_2OH), R_8-SH, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3, CH_2-O-CH_2-CH_2-O-CH_3, CH_2-O-CH_3), -O-R_8-O-R_{10} (e.g., O-CH_2-CH_2-O-CH_3), -R_8-O-R_6-R_{30} (e.g.,

CH_2O-tetrahydro-*2H*-pyrane, CH_2O-CH_2-CCH, CH_2O-CH_2CH_2O-CH_3, CH_2O-CH_2CH_2NH-CH_3, CH_2-O-CH_2CH_2S-CH_3, CH_2O-$CH_2CH_2S(O)CH_3$, CH_2O-$CH_2CH_2SO_2$-CH_3, CH_2O-CH_2CF_2H, CH_2-O-CH_2-CH_2-O-CH_3, CH_2O-CH_2-C(H)(OH)-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$ (e.g., CH_2-NH-CH_3, CH_2-NH-C(O)CH_3, CH_2-$N(CH_3)_2$), R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R (e.g., NHCO-Ph, NHCO-CH_3) , NHC(O)-R_{10} (e.g., NHCO-CH_3), NHCO-$N(R_{10})(R_{11})$, COOH, -C(O)Ph, C(O)O-R_{10}, R_8-C(O)-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -$C(O)NH_2$, C(O)NHR (e.g., C(O)NH-Ph), $C(O)N(R_{10})(R_{11})$, SO_2R, $SO_2N(R_{10})(R_{11})$, $NHSO_2(R_{10})$ (e.g., $NHSO_2CH_3$), $CH(CF_3)(NH\text{-}R_{10})$, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., azetidine, pyridine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl;

X_1, **X_2** **X_3**, **X_4** and **X_5** are each indepednetly C or N;

X_6 is O, CH_2, CHR (e.g., CH(OH), $CH(NH_2)$, $CH(NH(CH_3))$), $C(R_{10})(R_{11})$ (e.g., $C(H)CH_2CH_2$-OH, $C(H)CH_2$-OH, 1-methylazetidine), NH, N-$S(O)_2$-R_{10} (e.g., N-SO_2-CH_3), N-R (e.g., N-CH_3, N-SO_2-CH_3, N-R_{20}, N-CH_2CH_2-OCH_3,) or N-C(O)-R_{10} (e.g., N-C(O)O-tBu, N-C(O)-CH_2CH_2-OCH_3, N-C(O)-CH_3, N-C(O)-CH_2-$N(CH_3)_2$, N-C(O)-CH_2-CH_2-$N(CH_3)_2$, N-C(O)-CH_2-OH, N-C(O)-CH_2CH_2-OH, N-C(O)-NH-CH_3, N-C(O)-1-methyl-2-pyrrolidine, N-C(O)-1-methyl-3-pyrrolidine, N-C(O)-1-methyl-3-piperidine, N-C(O)-1-methyl-4-piperidine);

R_6 is **$[CH_2]_w$**

wherein **w** is between 0 and 10 (e.g., 0, 1, 2);

R_8 is **$[CH_2]_p$**

wherein **p** is between 1 and 10 (e.g., 2);

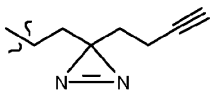
R_9 is $[CH]_q$, $[C]_q$

wherein **q** is between 2 and 10;

R_{10} and **R_{11}** are each independently H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., 1-(methylsulfonyl)piperidine, 1-(methylsulfonyl)piperazine, tetrahydro-*2H*-pyrane, morpholine, thiomorpholine 1,1-dioxide, methyl-pyrrolidine, methyl-piperidine), C(O)-alkyl, or $S(O)_2$-alkyl;

or **R_{10}** and **R_{11}** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, piperazine, piperidine, pyrrolidine, 1-methylpyrrolidin-2-one , oxetane, azetidine, 1-methylazetidine, 1-(piperazin-1-yl)ethanone),

R_{20} is represented by the following structure:



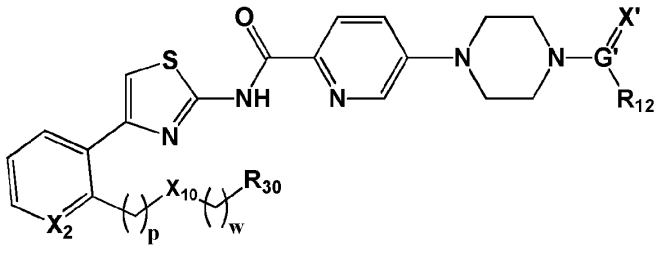
R_{30} is H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, C(H)(OH)(CH_3), methyl, ethyl, CH_2-CH_2-O-CH_3), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), C_1-C_5 linear or branched thioalkoxy (e.g., S-CH_3), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane), N(R_{10})(R_{11}) (e.g., N(H)(CH_3), S(O)R (e.g., S(O)-CH_3), SO_2R (e.g., SO_2-CH_3), or C(O)R;

R is H, OH, F, Cl, Br, I, CN, CF_3, NO_2, NH_2, NH(R_{10}) (e.g., NH(CH_3)), N(R_{10})(R_{11}), R_{20}, C_1-C_5 linear or branched, C_1-C_5 substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH_2CH_2OH, $CH_2CH_2OCH_3$), R_8-R_{10} (e.g., CH_2-OH, CH_2CH_2-OH), C(O)-R_{10} (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine, C(O)-CH_3), C_1-C_5 substituted or unsubstituted C(O)-alkyl (e.g., C(O)-CH_2CH_2-OCH_3, C(O)-CH_3, C(O)-CH_2-N(CH_3)$_2$, C(O)-CH_2-CH_2-N(CH_3)$_2$, C(O)-CH_2-OH), C(O)-R_8-R_{10} (e.g., C(O)-CH_2CH_2-OH), C(O)-substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine), C_1-C_5 substituted or unsubstituted SO_2-alkyl (e.g., SO_2-CH_3), C_1-C_5 substituted or unsubstituted C(O)-NH-alkyl (e.g., C(O)-NH-CH_3), C_1-C_5 linear or branched C(O)-O-alkyl (e.g., C(O)-O-tBu), C_1-C_5 linear or branched alkoxy, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine); or

two geminal **R** substitutions are joined together to form a 3 - 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopropyl, cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring;

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, reverse amide, pharmaceutical product or any combination thereof.

[0049] In various embodiments, this invention is directed to a compound represented by the structure of formula **IV**:



IV

wherein

X_2 is C or N;

X_{10} is O, S, NH, NR, N(H)C(O), C(O)NH, $S(O)_2NH$, $NHS(O)_2$;

w is between 0 and 10 (e.g., 0, 1, 2);

p is between 0 and 10 (e.g., 1);

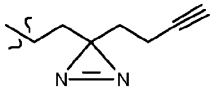
G'=X' is C=O, S=O or $S(O)_2$;

R_{10} and **R_{11}** are each independently H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., 1-(methylsulfonyl)piperidine, 1-(methylsulfonyl)piperazine, tetrahydro-*2H*-pyrane, morpholine, thiomorpholine 1,1-dioxide, methyl-pyrrolidine, methyl-piperidine), C(O)-alkyl, or $S(O)_2$-alkyl;

or **R_{10}** and **R_{11}** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, piperazine, piperidine, pyrrolidine, 1-methylpyrrolidin-2-one , oxetane, azetidine, 1-methylazetidine, 1-(piperazin-1-yl)ethanone);

R_{12} is H or substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl);

R_{20} is represented by the following structure:



;

R_{30} is H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, C(H)(OH)(CH_3), methyl, ethyl, CH_2-CH_2-O-CH_3), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), C_1-C_5 linear or branched thioalkoxy (e.g., S-CH_3), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane), N(R_{10})(R_{11}) (e.g., N(H)(CH_3), S(O)R (e.g., S(O)-CH_3), SO_2R (e.g., SO_2-CH_3), or C(O)R;

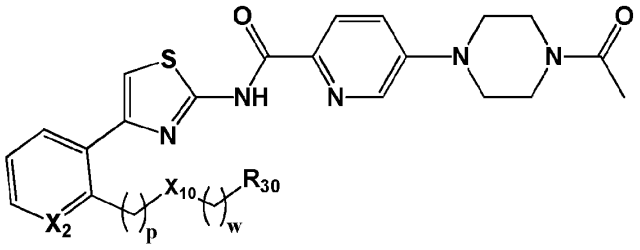
R is H, OH, F, Cl, Br, I, CN, CF_3, NO_2, NH_2, NH(R_{10}) (e.g., NH(CH_3)), N(R_{10})(R_{11}), R_{20}, C_1-C_5 linear or branched, C_1-C_5 substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH_2CH_2OH, $CH_2CH_2OCH_3$), R_8-R_{10} (e.g., CH_2-OH, CH_2CH_2-OH), C(O)-R_{10} (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine, C(O)-CH_3), C_1-C_5 substituted or unsubstituted C(O)-alkyl (e.g., C(O)-CH_2CH_2-OCH_3, C(O)-CH_3, C(O)-CH_2-N(CH_3)$_2$, C(O)-CH_2-CH_2-N(CH_3)$_2$, C(O)-CH_2-OH), C(O)-R_8-R_{10} (e.g., C(O)-CH_2CH_2-OH), C(O)-substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine), C_1-C_5 substituted or unsubstituted SO_2-alkyl (e.g., SO_2-CH_3), C_1-C_5 substituted or unsubstituted C(O)-NH-alkyl (e.g., C(O)-NH-CH_3), C_1-C_5 linear or branched C(O)-O-alkyl (e.g., C(O)-O-tBu), C_1-C_5 linear or branched alkoxy, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine); or

two geminal **R** substitutions are joined together to form a 3 - 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopropyl, cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring;

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, reverse amide, pharmaceutical product or any combination thereof.

[0050] In various embodiments, G'=X' is $S(O)_2$. In various embodiments, G'=X' is C(O). In various embodiments, $\mathbf{R_{12}}$ is C_1-C_5 linear or branched alkyl. In various embodiments, $\mathbf{R_{12}}$ is methyl. In various embodiments, (G'=X')($\mathbf{R_{12}}$) is C(O)-CH_3. In various embodiments, (G'=X')($\mathbf{R_{12}}$) is $S(O)_2$-CH_3. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)pyridin-3-yl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(hydroxymethyl)pyridin-3-yl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(hydroxymethyl)phenyl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide*. In various embodiments, the compound is not *N-(4-(2-(hydroxymethyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide*. In various embodiments, the compound is not *N-(4-(2-(acetamidomethyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide*. In various embodiments, the compound is not *N-(4-(2-(dimethylaminomethyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide*.

[0051] In various embodiments, this invention is directed to a compound represented by the structure of formula **IV(a)**:



IV(a)

wherein

$\mathbf{X_2}$ is C or N;

$\mathbf{X_{10}}$ is O, S, NH, NR, N(H)C(O), C(O)NH, $S(O)_2NH$, $NHS(O)_2$;

w is between 0 and 10 (e.g., 0, 1, 2);

p is between 0 and 10 (e.g., 1);

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independently H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., 1-(methylsulfonyl)piperidine, 1-

(methylsulfonyl)piperazine, tetrahydro-*2H*-pyrane, morpholine, thiomorpholine 1,1-dioxide, methyl-pyrrolidine, methyl-piperidine), C(O)-alkyl, or $S(O)_2$-alkyl;

or $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, piperazine, piperidine, pyrrolidine, 1-methylpyrrolidin-2-one , oxetane, azetidine, 1-methylazetidine, 1-(piperazin-1-yl)ethanone),

$\mathbf{R_{30}}$ is H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, C(H)(OH)(CH_3), methyl, ethyl, CH_2-CH_2-O-CH_3), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), C_1-C_5 linear or branched thioalkoxy (e.g., S-CH_3), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane), N(R_{10})(R_{11}) (e.g., N(H)(CH_3), S(O)R (e.g., S(O)-CH_3), SO_2R (e.g., SO_2-CH_3), or C(O)R;

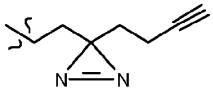
R is H, OH, F, Cl, Br, I, CN, CF_3, NO_2, NH_2, NH(R_{10}) (e.g., NH(CH_3)), N(R_{10})(R_{11}), R_{20}, C_1-C_5 linear or branched, C_1-C_5 substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH_2CH_2OH, $CH_2CH_2OCH_3$), R_8-R_{10} (e.g., CH_2-OH, CH_2CH_2-OH), C(O)-R_{10} (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine, C(O)-CH_3), C_1-C_5 substituted or unsubstituted C(O)-alkyl (e.g., C(O)-CH_2CH_2-OCH_3, C(O)-CH_3, C(O)-CH_2-N(CH_3)$_2$, C(O)-CH_2-CH_2-N(CH_3)$_2$, C(O)-CH_2-OH), C(O)-R_8-R_{10} (e.g., C(O)-CH_2CH_2-OH), C(O)-substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine), C_1-C_5 substituted or unsubstituted SO_2-alkyl (e.g., SO_2-CH_3), C_1-C_5 substituted or unsubstituted C(O)-NH-alkyl (e.g., C(O)-NH-CH_3), C_1-C_5 linear or branched C(O)-O-alkyl (e.g., C(O)-O-tBu), C_1-C_5 linear or branched alkoxy, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine); or

two geminal **R** substitutions are joined together to form a 3 - 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopropyl, cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring;

$\mathbf{R_8}$ is $\mathbf{[CH_2]_p}$

wherein **p** is between 1 and 10 (e.g., 1);

$\mathbf{R_{20}}$ is represented by the following structure:

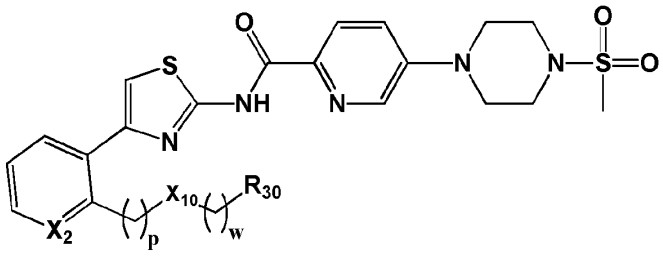


or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, reverse amide, pharmaceutical product or any combination thereof.

[0052] In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)pyridin-3-yl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide*. In various

embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(hydroxymethyl)pyridin-3-yl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(hydroxymethyl)phenyl)thiazol-2-yl)picolinamide*.

[0053] In various embodiments, this invention is directed to a compound represented by the structure of formula **IV(b)**:



IV(b)

wherein

$\mathbf{X_2}$ is C or N;

$\mathbf{X_{10}}$ is O, S, NH, NR, N(H)C(O), C(O)NH, $S(O)_2NH$, $NHS(O)_2$;

w is between 0 and 10 (e.g., 0, 1, 2);

p is between 0 and 10 (e.g., 1);

$\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are each independently H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., 1-(methylsulfonyl)piperidine, 1-(methylsulfonyl)piperazine, tetrahydro-*2H*-pyrane, morpholine, thiomorpholine 1,1-dioxide, methyl-pyrrolidine, methyl-piperidine), C(O)-alkyl, or $S(O)_2$-alkyl;

or $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, piperazine, piperidine, pyrrolidine, 1-methylpyrrolidin-2-one , oxetane, azetidine, 1-methylazetidine, 1-(piperazin-1-yl)ethanone),

$\mathbf{R_{30}}$ is H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, C(H)(OH)(CH_3), methyl, ethyl, CH_2-CH_2-O-CH_3), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), C_1-C_5 linear or branched thioalkoxy (e.g., S-CH_3), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane), N(R_{10})(R_{11}) (e.g., N(H)(CH_3), S(O)R (e.g., S(O)-CH_3), SO_2R (e.g., SO_2-CH_3), or C(O)R;

R is H, OH, F, Cl, Br, I, CN, CF_3, NO_2, NH_2, NH(R_{10}) (e.g., NH(CH_3)), N(R_{10})(R_{11}), R_{20}, C_1-C_5 linear or branched, C_1-C_5 substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH_2CH_2OH, $CH_2CH_2OCH_3$), R_8-R_{10} (e.g., CH_2-OH, CH_2CH_2-OH), C(O)-R_{10} (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine, C(O)-CH_3), C_1-C_5 substituted or unsubstituted C(O)-alkyl (e.g., C(O)-CH_2CH_2-OCH_3, C(O)-CH_3, C(O)-CH_2-N(CH_3)$_2$, C(O)-CH_2-CH_2-N(CH_3)$_2$, C(O)-CH_2-OH), C(O)-R_8-R_{10} (e.g., C(O)-CH_2CH_2-OH), C(O)-substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., C(O)-

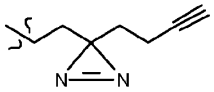
methylpyrroldine, C(O)-methylpiperidine), C_1-C_5 substituted or unsubstituted SO_2-alkyl (e.g., SO_2-CH_3), C_1-C_5 substituted or unsubstituted C(O)-NH-alkyl (e.g., C(O)-NH-CH_3), C_1-C_5 linear or branched C(O)-O-alkyl (e.g., C(O)-O-tBu), C_1-C_5 linear or branched alkoxy, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine); or

two geminal **R** substitutions are joined together to form a 3 - 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopropyl, cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring;

$\mathbf{R_8}$ is $\mathbf{[CH_2]_p}$

wherein **p** is between 1 and 10 (e.g., 1);

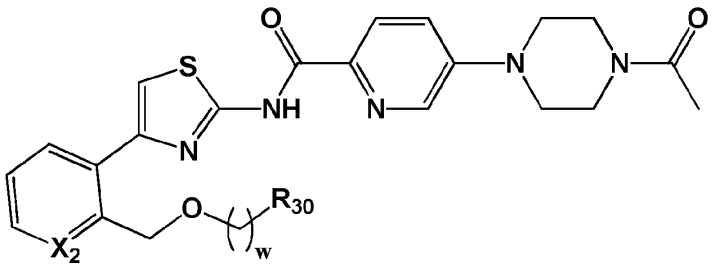
$\mathbf{R_{20}}$ is represented by the following structure:



or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, reverse amide, pharmaceutical product or any combination thereof.

[0054] In various embodiments, the compound is not *N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide*. In various embodiments, the compound is not *N-(4-(2-(hydroxymethyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide*. In various embodiments, the compound is not *N-(4-(2-(acetamidomethyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide*. In various embodiments, the compound is not *N-(4-(2-(dimethylaminomethyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide*.

[0055] In various embodiments, this invention is directed to a compound represented by the structure of formula **V**:



V

wherein

$\mathbf{X_2}$ is C or N;

w is between 0 and 10 (e.g., 0, 1, 2);

R_{30} is H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, C(H)(OH)(CH_3), methyl, ethyl, CH_2-CH_2-O-CH_3), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), C_1-C_5 linear or branched thioalkoxy (e.g., S-CH_3), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane), N(R_{10})(R_{11}) (e.g., N(H)(CH_3), S(O)R (e.g., S(O)-CH_3), SO_2R (e.g., SO_2-CH_3), or C(O)R;

R_{10} and **R_{11}** are each independently H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., 1-(methylsulfonyl)piperidine, 1-(methylsulfonyl)piperazine, tetrahydro-*2H*-pyrane, morpholine, thiomorpholine 1,1-dioxide, methyl-pyrrolidine, methyl-piperidine), C(O)-alkyl, or S($O)_2$-alkyl;

or **R_{10}** and **R_{11}** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., morpholine, piperazine, piperidine, pyrrolidine, 1-methylpyrrolidin-2-one , oxetane, azetidine, 1-methylazetidine, 1-(piperazin-1-yl)ethanone),

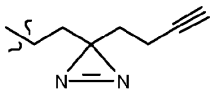
R is H, OH, F, Cl, Br, I, CN, CF_3, NO_2, NH_2, NH(R_{10}) (e.g., NH(CH_3)), N(R_{10})(R_{11}), R_{20}, C_1-C_5 linear or branched, C_1-C_5 substituted or unsubstituted alkyl (e.g., methyl, ethyl, CH_2CH_2OH, $CH_2CH_2OCH_3$), R_8-R_{10} (e.g., CH_2-OH, CH_2CH_2-OH), C(O)-R_{10} (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine, C(O)-CH_3), C_1-C_5 substituted or unsubstituted C(O)-alkyl (e.g., C(O)-CH_2CH_2-OCH_3, C(O)-CH_3, C(O)-CH_2-N($CH_3)_2$, C(O)-CH_2-CH_2-N($CH_3)_2$, C(O)-CH_2-OH), C(O)-R_8-R_{10} (e.g., C(O)-CH_2CH_2-OH), C(O)-substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., C(O)-methylpyrroldine, C(O)-methylpiperidine), C_1-C_5 substituted or unsubstituted SO_2-alkyl (e.g., SO_2-CH_3), C_1-C_5 substituted or unsubstituted C(O)-NH-alkyl (e.g., C(O)-NH-CH_3), C_1-C_5 linear or branched C(O)-O-alkyl (e.g., C(O)-O-tBu), C_1-C_5 linear or branched alkoxy, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3), C_1-C_5 linear or branched haloalkyl (e.g., CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$,$CF(CH_3)$-$CH(CH_3)_2$), R_8-aryl (e.g., CH_2-Ph), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine); or

two geminal **R** substitutions are joined together to form a 3 - 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopropyl, cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring;

R_8 is **$[CH_2]_p$**

wherein **p** is between 1 and 10 (e.g., 1);

R_{20} is represented by the following structure:



or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, reverse amide, pharmaceutical product or any combination thereof.

[0056] In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)pyridin-3-yl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(hydroxymethyl)pyridin-3-yl)thiazol-2-yl)picolinamide*. In various embodiments, the compound is not *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(hydroxymethyl)phenyl)thiazol-2-yl)picolinamide*.

[0057] In some embodiments, **A** of formula **I** is a phenyl. In other embodiments, A is pyridinyl. In other embodiments, A is 2-pyridinyl. In other embodiments, A is 3-pyridinyl. In other embodiments, A is either phenyl or pyridinyl. In other embodiments, A is either phenyl or 3-pyridinyl. In other embodiments, A is In other embodiments, A is 4-pyridinyl.

[0058] In some embodiments, **B** of formula **I** is a phenyl ring. In other embodiments, B is pyridinyl. In other embodiments, B is 2-pyridinyl. In other embodiments, B is 3-pyridinyl. In other embodiments, B is 4-pyridinyl.

[0059] In various embodiments, compound of formula **I-III** is substituted by $\mathbf{R_1}$. In various embodiments, compound of formula **I** is substituted by $\mathbf{R_2}$. In various embodiments, compound of formula **I-II** is substituted by $\mathbf{R_3}$. In various embodiments, compound of formula **I** is substituted by $\mathbf{R_4}$. Single substituents can be present at the *ortho*, *meta*, or *para* positions.

[0060] In some embodiments, at least one of $\mathbf{R_2}$ and $\mathbf{R_4}$ of compound of formula **I** is H. In some embodiments, both $\mathbf{R_2}$ and $\mathbf{R_4}$ of compound of formula **I** are H. In some embodiments, $\mathbf{R_2}$ of compound of formula **I** is H. In some embodiments, $\mathbf{R_4}$ of compound of formula **I** is H. In some embodiments, at least one of $\mathbf{R_1}$ and $\mathbf{R_3}$ of compound of formula **I-II** are not H. In some embodiments, both $\mathbf{R_1}$ and $\mathbf{R_3}$ of compound of formula **I-II** are not H. In some embodiments, $\mathbf{R_1}$ of compound of formula **III** is not H. In some embodiments, $\mathbf{R_3}$ of compound of formula **I** or **II** is not H.

[0061] In some embodiments, $\mathbf{R_1}$ of compound of formula **I** is in the *ortho* position. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is $-R_8-O-R_6-R_{30}$. In some embodiments, $-R_8-O-R_6-R_{30}$ is CH_2O-tetrahydro-*2H*-pyrane. In some embodiments, $-R_8-O-R_6-R_{30}$ is CH_2O-CH_2-CCH. In some embodiments, $-R_8-O-R_6-R_{30}$ is $CH_2O-CH_2CH_2O-CH_3$. In some embodiments, $-R_8-O-R_6-R_{30}$ is $CH_2O-CH_2CH_2NH-CH_3$. In some embodiments, $-R_8-O-R_6-R_{30}$ is $CH_2O-CH_2CH_2S-CH_3$. In some embodiments, $-R_8-O-R_6-R_{30}$ is $CH_2O-CH_2CH_2S(O)CH_3$. In some embodiments, $-R_8-O-R_6-R_{30}$ is $CH_2O-CH_2CH_2SO_2-CH_3$. In some embodiments, $-R_8-O-R_6-R_{30}$ is $CH_2O-CH_2CF_2H$. In some embodiments, $-R_8-O-R_6-R_{30}$ is $CH_2-O-CH_2-CH_2-O-CH_3$. In some embodiments, $-R_8-O-R_6-R_{30}$ is $CH_2O-CH_2-C(H)(OH)-CH_3$). In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is $-R_8-O-R_6-R_{30}$ wherein $\mathbf{R_8}$ is CH_2. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is $-R_8-O-R_6-R_{30}$ wherein $\mathbf{R_8}$ is CH_2 and $\mathbf{R_6}$ is CH_2-CH_2 (i.e., **w** is 2). In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is $-R_8-O-R_6-R_{30}$ wherein $\mathbf{R_8}$ is CH_2, $\mathbf{R_6}$ is absent (i.e., **w** is 0) and $\mathbf{R_{30}}$ is tetrahydro-*2H*-pyrane. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is $-R_8-O-R_6-R_{30}$, wherein $\mathbf{R_8}$ is CH_2 and $\mathbf{R_{30}}$ is tetrahydro-*2H*-pyrane. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is $-R_8-O-R_6-R_{30}$ wherein $\mathbf{R_8}$ is CH_2, $\mathbf{R_6}$ is CH_2CH_2 (i.e., **w** is 2), and $\mathbf{R_{30}}$ is OCH_3, $N(H)CH_3$, $S-CH_3$, $S(O)CH_3$, $S(O)_2CH_3$; each is a separate embodiment

according to this invention. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is -R_8-O-R_6-R_{30} wherein $\mathbf{R_8}$ is CH_2, $\mathbf{R_6}$ is CH_2 (i.e., **w** is 1), and $\mathbf{R_{30}}$ is methyl, CCH, CF_2H, or C(H)(OH)-CH_3; each is a separate embodiment according to this invention. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is -R_8-O-R_{10}. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is -R_8-O-R_{10} wherein $\mathbf{R_8}$ is CH_2. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is -R_8-O-R_{10} wherein $\mathbf{R_{10}}$ is tetrahydro-*2H*-pyrane. In some embodiments, $\mathbf{R_1}$ of compound of formula **I-III** is -R_8-O-R_{10} wherein $\mathbf{R_8}$ is CH_2 and $\mathbf{R_{10}}$ is tetrahydro-*2H*-pyrane.

[0062] In some embodiments, $\mathbf{R_2}$ of compound of formula **I** is H.

[0063] In some embodiments, $\mathbf{R_3}$ of compound of formula **I-II** is a substituted or unsubstituted, single, spirocyclic, fused, or bridged C_3-C_{10} heterocycle. In some embodiments, $\mathbf{R_3}$ is a substituted piperazine. In some embodiments, $\mathbf{R_3}$ is a 1-(piperazin-1-yl)ethanone. In some embodiments, $\mathbf{R_3}$ is 1- or 4-(methylsulfonyl)piperazine. In some embodiments, $\mathbf{R_3}$ is $N(R_{10})(R_{11})$. In some embodiments, $\mathbf{R_1}$ is R_8-O-R_6-R_{30} and $\mathbf{R_3}$ is $N(R_{10})(R_{11})$. In some embodiments, $N(R_{10})(R_{11})$ is a substituted or unsubstituted 3-8 membered heterocycle. In some embodiments, $N(R_{10})(R_{11})$ is a substituted or unsubstituted 6-membered ring heterocycle. In some embodiments, $N(R_{10})(R_{11})$ is amide substituted piperazine (e.g., 1- or 4-(methylsulfonyl)piperazine, *N*-methylpiperazine-1-carboxamide or 1-(piperazin-1-yl)ethanone) sulphonyl substituted piperazine (e.g., 1- or 4-(methylsulfonyl)piperazine); each is a separate embodiment according to this invention. In some embodiments, $N(R_{10})(R_{11})$ is 1-(piperazin-1-yl)ethenone. In some embodiments, $N(R_{10})(R_{11})$ is 1- or 4-(methylsulfonyl)piperazine. In some embodiments, $\mathbf{R_1}$ is -R_8-O-R_6-R_{30} and $\mathbf{R_3}$ is 1-(piperazin-1-yl)ethenone. In some embodiments, $\mathbf{R_1}$ is -R_8-O-R_{10} and $\mathbf{R_3}$ is 1-(piperazin-1-yl)ethenone.

[0064] In some embodiments, if R_3 is a heterocycle, then R_1 cannot be H. In some embodiments, if R_3 is a heterocycle, then R_1 is -R_8-O-R_{10}. In some embodiments, if R_3 is a heterocycle, then R_1 is -R_8-O-R_6-R_{30}.

[0065] In some embodiments, $\mathbf{R_4}$ of compound of formula **I** is H.

[0066] In some embodiments, $\mathbf{R_5}$ of compound of formula **I** is H.

[0067] In some embodiments, $\mathbf{R_6}$ of compound of formula **I-III** is absent (i.e., w is 0). In some embodiments, $\mathbf{R_6}$ is CH_2 (i.e., w is 1). In some embodiments, $\mathbf{R_6}$ is CH_2CH_2 (i.e., w is 2).

[0068] In some embodiments, **w** of compound of formula **I-V** is 0. In some embodiments, **w** is 1. In some embodiments, **w** is 2. In some embodiments, **w** is 3. In some embodiments, **w** is 4. In some embodiments, **w** is 5.

[0069] In some embodiments, $\mathbf{R_8}$ of compound of formula **I-V** is CH_2 (i.e., p is 1). In some embodiments, $\mathbf{R_8}$ is CH_2CH_2 (i.e., p is 2).

[0070] In some embodiments, **p** of compound of formula **I-V** is 1. In some embodiments, **p** is 2. In some embodiments, **p** is 3. In some embodiments, **p** is 0.

[0071] In some embodiments, $\mathbf{R_{10}}$ of formula **I-V** is is substituted or unsubstituted 3-8 membered heterocyclic ring. In other embodiments, R_{10} is tetrahydro-*2H*-pyrane.

[0072] In some embodiments, $\mathbf{R_{11}}$ of formula **I-V** is H.

[0073] In some embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ of formula **I-V** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a substituted piperazine ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form 1-(piperazin-1-yl)ethanone. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form 1- or 4-(methylsulfonyl)piperazine. In some embodiments, substitutions include: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., C(O)-CH_3, C(O)-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl, (benzyloxy)phenyl or any combination thereof; each represents a separate embodiment according to this invention.

[0074] In some embodiments, $\mathbf{R_{12}}$ of formula **IV** is a substituted or unsubstituted C_1-C_5 linear alkyl. In some embodiments, $\mathbf{R_{12}}$ is unsubstituted C_1-C_5 branched alkyl. In some embodiments, $\mathbf{R_{12}}$ is substituted C_1-C_5 branched alkyl. In some embodiments, $\mathbf{R_{12}}$ is substituted C_1-C_5 branched alkyl. In some embodiments, $\mathbf{R_{12}}$ is unsubstituted C_1-C_5 branched alkyl. In some embodiments, $\mathbf{R_{12}}$ is methyl. In some embodiments, $\mathbf{R_{12}}$ is ethyl. In some embodiments, the alkyl may be substituted with at least one substituent, selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, OH, C_1-C_5 linear or branched alkoxy, cyclic alkoxy, amide (i.e., C(O)-NH-alkyl or NH-C(O)-alkyl), $C(O)N(R_{10})(R_{11})$, amine (i.e., $NH(R_{10})$, $N(R_{10})(R_{11})$, NH_2), aryl, phenyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted 3-8 membered heterocyclic ring, which may be saturated, unsaturated, aromatic, single, fused, bridged or spiral; each represents a separate embodiment according to this invention.

[0075] In some embodiments, **G=X** of compound of formula **I** is C=O.

[0076] In some embodiments, **G'=X'** of compound of formula **IV** is C=O. In some embodiments, **G'=X'** is $S(O)_2$. In some embodiments, **G'=X'** is S(O).

[0077] In some embodiments, $\mathbf{Q_1}$ of compound of formula **I** is S.

[0078] In some embodiments, $\mathbf{R_{30}}$ of formula **I-V** is substituted or unsubstituted C_1-C_5 linear or branched alkyl. In some embodiments, the alkyl may be further substituted with at least one selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, C_1-C_5 linear or branched alkoxy (e.g. OCH_3), C_2-C_5 linear or branched alkynyl (e.g. CCH), C_1-C_5 linear or branched thioalkoxy (e.g. SCH_3), C_1-C_5 linear or branched alkylsulfinyl (e.g. S(O)CH_3), C_1-C_5 linear or branched alkylsulfonyl (e.g. $S(O)_2$-CH_3), NH_2, C_1-C_5 linear or branched N(H)(alkyl) (e.g., N(H)(CH_3)), and C_1-C_5 linear or branched $N(alkyl)_2$; each represents a separate embodiment according to this invention. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is C(H)(OH)(CH_3). In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is methyl. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is ethyl. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-O-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-O-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-S-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-S-CH_3. In some embodiments, the substituted

or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-S(O)-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-S(O)-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-$S(O)_2$-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-$S(O)_2$-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-NH-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-NH-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CCH. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CHF_2. In some embodiments, $\mathbf{R_{30}}$ is C_2-C_5 linear or branched, substituted or unsubstituted alkynyl. In some embodiments, the C_2-C_5 linear or branched, substituted or unsubstituted alkynyl is CCH. In some embodiments, $\mathbf{R_{30}}$ is C_1-C_5 linear or branched alkoxy. In some embodiments, the C_1-C_5 linear or branched alkoxy is O-CH_3. In some embodiments, $\mathbf{R_{30}}$ is C_1-C_5 linear or branched thioalkoxy. In some embodiments, the C_1-C_5 linear or branched thioalkoxy is S-CH_3. In some embodiments, $\mathbf{R_{30}}$ is C_1-C_5 linear, branched or cyclic haloalkyl. In some embodiments, the C_1-C_5 linear, branched or cyclic haloalkyl is CHF_2. In some embodiments, $\mathbf{R_{30}}$ is substituted or unsubstituted 3-8 membered heterocyclic ring. In some embodiments, the substituted or unsubstituted 3-8 membered heterocyclic ring is tetrahydro-*2H*-pyrane. In some embodiments, $\mathbf{R_{30}}$ is N(R_{10})(R_{11}). In some embodiments, N(R_{10})(R_{11}) is N(H)(CH_3). In some embodiments, $\mathbf{R_{30}}$ is S(O)R. In some embodiments, S(O)R is S(O)-CH_3. In some embodiments, $\mathbf{R_{30}}$ is SO_2R. In some embodiments, SO_2R is SO_2-CH_3.

[0079] In some embodiments, at least one of $\mathbf{X_2}$, $\mathbf{X_3}$, $\mathbf{X_4}$ and $\mathbf{X_5}$ of formula **II-III** is N. In some embodiments, at least two of $\mathbf{X_2}$, $\mathbf{X_3}$, $\mathbf{X_4}$ and $\mathbf{X_5}$ are N. In some embodiments, $\mathbf{X_2}$ and $\mathbf{X_3}$ of formula **II-III** are both N.

[0080] In some embodiments, $\mathbf{X_1}$ of compound of formula **II - III** is N. In other embodiments, $\mathbf{X_1}$ is C.

[0081] In some embodiments, $\mathbf{X_2}$ of compound of formula **II - V** is N. In other embodiments, $\mathbf{X_2}$ is C.

[0082] In some embodiments, $\mathbf{X_3}$ of compound of formula **II - III** is N. In other embodiments, $\mathbf{X_3}$ is C.

[0083] In some embodiments, both $\mathbf{X_2}$ and $\mathbf{X_3}$ of compound of formula **II - III** are N.

[0084] In some embodiments, $\mathbf{X_4}$ of compound of formula **II - III** is N. In other embodiments, $\mathbf{X_4}$ is C.

[0085] In some embodiments, $\mathbf{X_5}$ of compound of formula **II - III** is N. In other embodiments, $\mathbf{X_5}$ is C.

[0086] It is understood that H atoms are added where necessary, in order to complete the valence of the unsubstituted carbon atoms of $\mathbf{X_1}$-$\mathbf{X_5}$ of any one of formulas **II-V**.

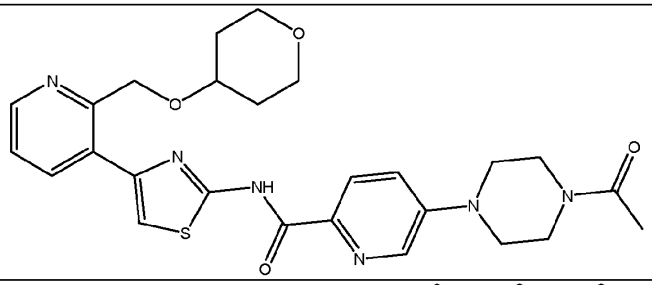
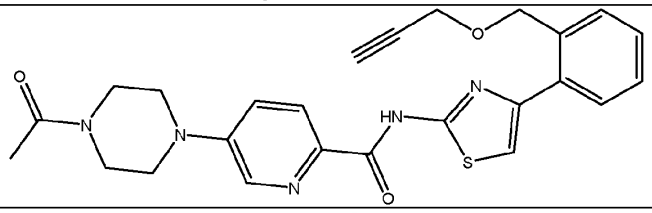
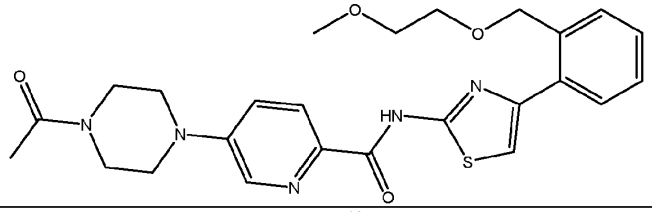
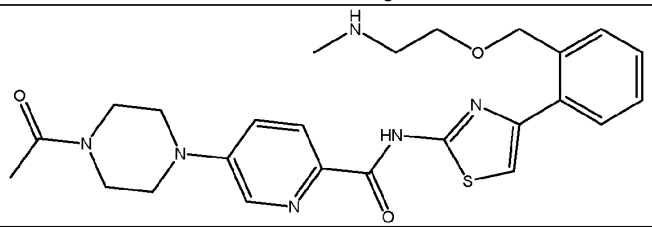
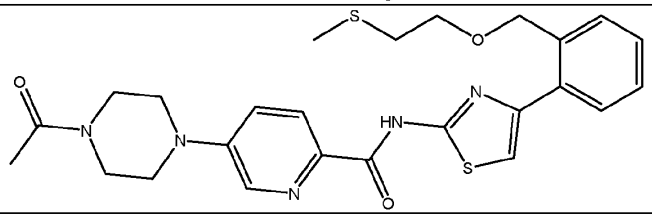
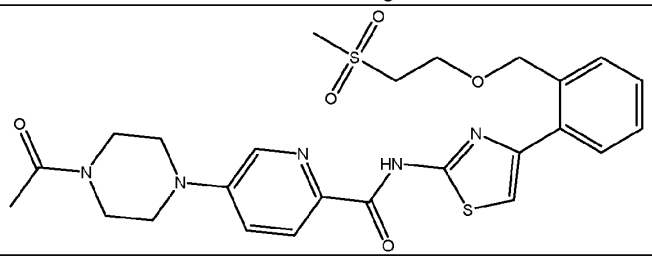
[0087] It is understood that if any of $\mathbf{X_1}$-$\mathbf{X_5}$ are N, then any of $\mathbf{R_1}$-$\mathbf{R_4}$ cannot be attached thereto.

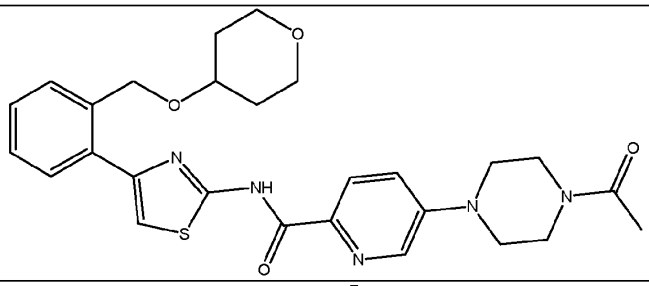
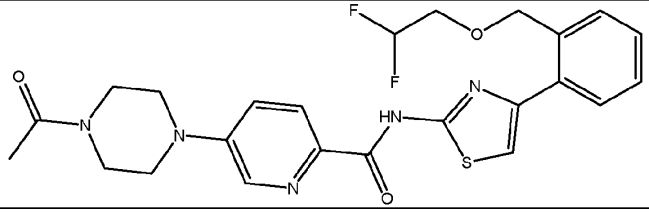
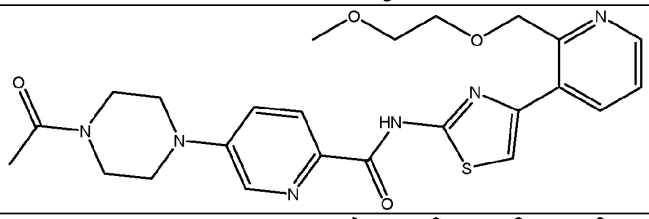
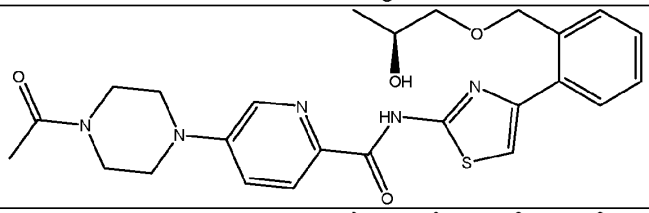
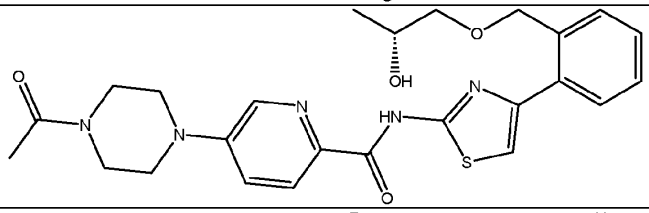
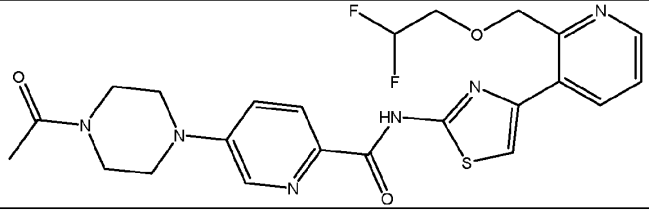
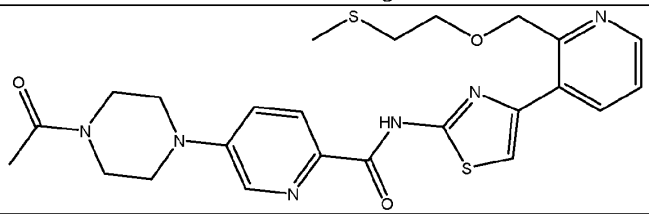
[0088] In some embodiments, $\mathbf{X_6}$ of compound of formula **III** is N-C(O)-R_{10}. In other embodiments, $\mathbf{X_6}$ is N-C(O)-CH_3. In other embodiments, $\mathbf{X_6}$ is N-R. In other embodiments, R is C_1-C_5 substituted or unsubstituted SO_2-alkyl. In other embodiments, **R** is SO_2-CH_3. In other embodiments, $\mathbf{X_6}$ is N-$S(O)_2$-R_{10}. In other embodiments, $\mathbf{X_6}$ is N-SO_2-CH_3.

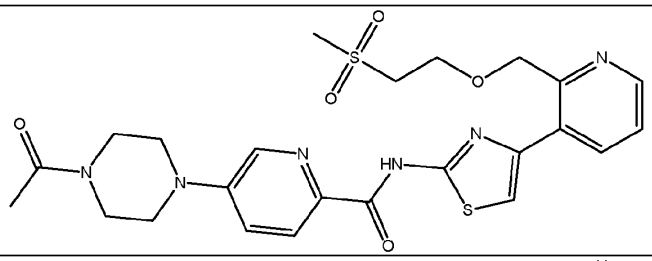
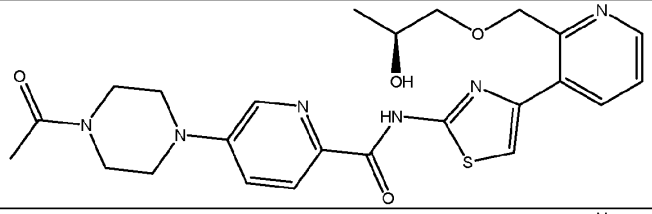
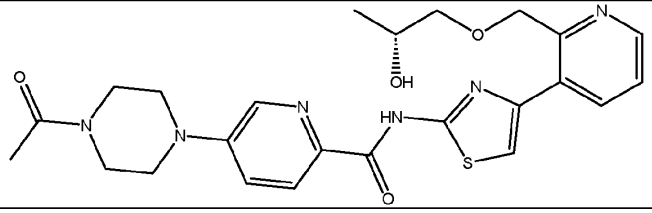
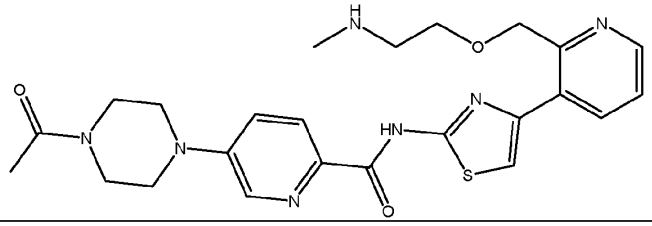
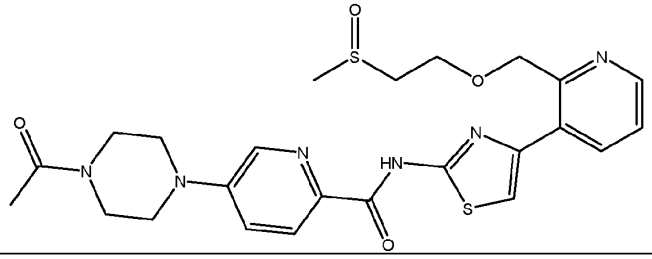
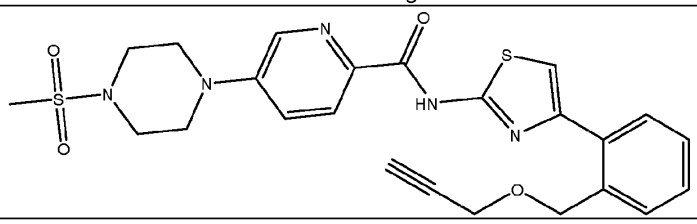
[0089] In some embodiments, $\mathbf{X_{10}}$ of compound of formula **IV, IV(a)** and/or **IV(b)** is O. In some embodiments, $\mathbf{X_{10}}$ is S. In some embodiments, $\mathbf{X_{10}}$ is NH. In some embodiments, $\mathbf{X_{10}}$ is N(H)C(O).

[0090] In various embodiments, this invention is directed to the compounds presented in Table 1, pharmaceutical compositions and/or method of use thereof, each represents a separate embodiment according to this invention:

Table 1:

Compound Number	Compound Structure
100	
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[0091] It is well understood that in structures presented in this invention wherein the carbon atom has less than 4 bonds, H atoms are present to complete the valence of the carbon. It is well understood that in structures presented in this invention wherein the nitrogen atom has less than 3 bonds, H atoms are present to complete the valence of the nitrogen.

[0092] In some embodiments, this invention is directed to the compounds listed hereinabove, pharmaceutical compositions and/or method of use thereof, wherein the compound is pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, prodrug, isotopic variant (deuterated analog), PROTAC, pharmaceutical product or any combination thereof. In some embodiments, the compounds are Collagen I translation inhibitors. In some embodiments, the compounds are Collagen I, II, II, IV, or V translation inhibitors; each represents a separate embodiment according to this invention. In some embodiments, the compounds are selective to Collagen I, II, II, IV, or V; each represents a separate embodiment according to this invention. In some embodiments, the compounds are selective to Collagen I. In some embodiments, the compounds are selective to Collagen IA. In some embodiments, the compounds are selective to Collagen IA1.

Other Embodiments According to The Invention

[0093] In various embodiments, the **A** ring of formula **I** is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, 1-methylimidazole, isoquinoline, pyrazolyl, pyrrolyl, furanyl, thiophene-yl, isoquinolinyl, indolyl, 1H-indole, isoindolyl, naphthyl, anthracenyl, benzimidazolyl, indazolyl, 2H-indazole, triazolyl, 4,5,6,7-tetrahydro-2H-indazole, 3H-indol-3-one, purinyl, benzoxazolyl, 1,3-benzoxazolyl, benzisoxazolyl, benzothiazolyl, 1,3-benzothiazole, 4,5,6,7-tetrahydro-1,3-benzothiazole, quinazolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinolinyl, isoquinolinyl, 2,3-dihydroindenyl, indenyl, tetrahydronaphthyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepine , benzo[d][1,3]dioxole, acridinyl, benzofuranyl, 1-benzofuran, isobenzofuranyl, benzofuran-2(3H)-one, benzothiophenyl, benzoxadiazole, benzo[c][1,2,5]oxadiazolyl, benzo[*c*]thiophenyl, benzodioxolyl, benzo[d][1,3]dioxole, thiadiazolyl, [1,3]oxazolo[4,5-b]pyridine, oxadiaziolyl, imidazo[2,1-b][1,3]thiazole, 4H,5H,6H-cyclopenta[d][1,3]thiazole, 5H,6H,7H,8H-imidazo[1,2-a]pyridine, 7-oxo-6H,7H-[1,3]thiazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-b]pyridine, 2H,3H-imidazo[2,1-b][1,3]thiazole, thieno[3,2-d]pyrimidin-4(3H)-one, 4-oxo-4H-thieno[3,2-d][1,3]thiazin, imidazopyridin, imidazo[1,2-a]pyridine, 1H-imidazo[4,5-b]pyridine, 1H-imidazo[4,5-c]pyridine, 3H-imidazo[4,5-c]pyridine, pyrazolopyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, 1H-pyrrolo[2,3-b]pyridine, pyrido[2,3-b]pyrazine, pyrido[2,3-b]pyrazin-3(4H)-one, 4H-thieno[3,2-b]pyrrole, quinoxalin-2(1H)-one, pyrrolopyridine, 1H-pyrrolo[3,2-b]pyridine, 7H-pyrrolo[2,3-d]pyrimidine, oxazolo[5,4-b]pyridine, thiazolo[5,4-b]pyridine, thieno[3,2-c]pyridine; each represents a separate embodiment according to this invention; or **A** is C_3-C_8 cycloalkyl (e.g. cyclohexyl, cyclopentyl, bicyclo[1.1.1]pentyl, cyclobutyl) or 3-8 membered heterocyclic ring including but not limited to: tetrahydropyran, piperidine, 1-methylpiperidine, tetrahydrothiophene 1,1-dioxide, pyrrolidin-2-one, piperazine, 1-(piperidin-1-yl)ethanone or morpholine; each represents a separate embodiment according to this invention. In some embodiments, **A** is a phenyl. In some embodiments, **A** is a pyridinyl. In some embodiments, **A** is 3-pyridinyl.

[0094] In various embodiments, the **B** ring of formula **I** is phenyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, 1-methylimidazole, isoquinoline, pyrazolyl, pyrrolyl, furanyl, thiophene-yl, isoquinolinyl, indolyl, 1H-

indole, isoindolyl, naphthyl, anthracenyl, benzimidazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, tetrahydronaphthyl 3,4-dihydro-2H-benzo[b][1,4]dioxepine, benzofuran-2(3H)-one, benzo[d][1,3]dioxole, indazolyl, 2H-indazole, triazolyl, 4,5,6,7-tetrahydro-2H-indazole, 3H-indol-3-one, purinyl, benzoxazolyl, 1,3-benzoxazolyl, benzisoxazolyl, benzothiazolyl, 1,3-benzothiazole, 4,5,6,7-tetrahydro-1,3-benzothiazole, quinazolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinolinyl, isoquinolinyl, acridinyl, benzofuranyl, 1-benzofuran, isobenzofuranyl, benzothiophenyl, benzoxadiazole, benzo[c][1,2,5]oxadiazolyl, benzo[*c*]thiophenyl, benzodioxolyl, thiadiazolyl, [1,3]oxazolo[4,5-b]pyridine, oxadiaziolyl, imidazo[2,1-b][1,3]thiazole, 4H,5H,6H-cyclopenta[d][1,3]thiazole, 5H,6H,7H,8H-imidazo[1,2-a]pyridine, 7-oxo-6H,7H-[1,3]thiazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-b]pyridine, 2H,3H-imidazo[2,1-b][1,3]thiazole, thieno[3,2-d]pyrimidin-4(3H)-one, 4-oxo-4H-thieno[3,2-d][1,3]thiazin, imidazo[1,2-a]pyridine, 1H-imidazo[4,5-b]pyridine, 3H-imidazo[4,5-b]pyridine, 3H-imidazo[4,5-c]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, pyrido[2,3-b]pyrazin or pyrido[2,3-b]pyrazin-3(4H)-one, 4H-thieno[3,2-b]pyrrole, quinoxalin-2(1H)-one, 1,2,3,4-tetrahydroquinoxaline, 1-(pyridin-1(2H)-yl)ethanone,1H-pyrrolo[2,3-b]pyridine, 1H-pyrrolo[3,2-b]pyridine, 7H-pyrrolo[2,3-d]pyrimidine, oxazolo[5,4-b]pyridine, thiazolo[5,4-b]pyridine, thieno[3,2-c]pyridine, C_3-C_8 cycloalkyl, or 3-8 membered heterocyclic ring including but not limited to: tetrahydropyran, piperidine, 1-methylpiperidine, tetrahydrothiophene 1,1-dioxide, 1-(piperidin-1-yl)ethanone, bicyclo[1.1.1]pentyl, cyclobutyl, cyclohexyl or morpholine; each represents a separate embodiment according to this invention. In some embodiments, **B** is a pyridinyl. In some embodiments, **B** is a 2-pyridinyl.

[0095] In various embodiments, $\mathbf{R_1}$ of formula **I-III** and/or $\mathbf{R_2}$ of formula **I** are each independently H. In some embodiments, $\mathbf{R_1}$ is not H. In some embodiments, $\mathbf{R_1}$ is Cl. In some embodiments, $\mathbf{R_1}$ is F. In some embodiments, $\mathbf{R_1}$ is R_8-OH. In some embodiments, $\mathbf{R_1}$ is CH_2OH. In some embodiments, $\mathbf{R_1}$ is -R_8-O-R_{10}. In some embodiments $\mathbf{R_{10}}$ is tetrahydro-*2H*-pyrane. In some embodiments, $\mathbf{R_1}$ is -R_8-O-R_{10}, wherein $\mathbf{R_{10}}$ is tetrahydro-*2H*-pyrane. In some embodiments, $\mathbf{R_1}$ is CH_2-O-CH_2-CH_2-O-CH_3.

[0096] In various embodiments, $\mathbf{R_1}$ of formula **I-III** and/or $\mathbf{R_2}$ of formula **I** are each independently F, Cl, Br, I, OH, SH, R_8-OH (e.g. CH_2OH), R_8-SH, -R_8-O-R_{10} (e.g., CH_2-CH_2-O-CH_3, CH_2-O-CH_2-CH_2-O-CH_3, CH_2-O-CH_3), -O-R_8-O-R_{10} (e.g., O-CH_2-CH_2-O-CH_3), -R_8-O-R_6-R_{30} (e.g., CH_2O-tetrahydro-*2H*-pyrane, CH_2O-CH_2-CCH, CH_2O-CH_2CH_2O-CH_3, CH_2O-CH_2CH_2NH-CH_3, CH_2O-CH_2CH_2S-CH_3, CH_2O-$CH_2CH_2S(O)CH_3$, CH_2O-$CH_2CH_2SO_2$-CH_3, CH_2O-CH_2CF_2H, CH_2-O-CH_2-CH_2-O-CH_3, CH_2O-CH_2-C(H)(OH)-CH_3), R_8-(C_3-C_8 cycloalkyl), R_8-(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-N(R_{10})(R_{11}) (e.g., CH_2-NH-CH_3, CH_2-NH-C(O)CH_3, CH_2-N(CH_3)$_2$), R_9-R_8-N(R_{10})(R_{11}), $B(OH)_2$, -OC(O)CF_3, -OCH_2Ph, NHC(O)-R (e.g., NHCO-Ph, NHCO-CH_3) , NHC(O)-R_{10} (e.g., NHCO-CH_3), NHCO-N(R_{10})(R_{11}), COOH, -C(O)Ph, C(O)O-R_{10}, R_8-C(O)-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -C(O)NH_2, C(O)NHR (e.g., C(O)NH-Ph), C(O)N(R_{10})(R_{11}), SO_2R, $SO_2N(R_{10})(R_{11})$, $NHSO_2(R_{10})$ (e.g., $NHSO_2CH_3$), $CH(CF_3)$(NH-R_{10}), C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear, branched or cyclic haloalkyl, CHF_2, C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2)

in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., azetidine, pyridine), substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted benzyl; each possibility represents a separate embodiment according to this invention. In some embodiment, R_1 and/or R_2 may be further substituted by at least one substituent selected from: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., C(O)-CH_3, C(O)-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl and (benzyloxy)phenyl; each possibility represents a separate embodiment according to this invention.

[0097] In some embodiments, **R_2** of formula **I** is H. In some embodiments, R_2 is Cl. In some embodiments, R_2 is F. In some embodiments, R_2 is R_8-OH. In some embodiments, R_2 is CH_2OH. In some embodiments, R_2 is -R_8-O-R_{10}. In some embodiments, R_2 is CH_2-O-CH_2-CH_2-O-CH_3. In some embodiments, R_2 is CH_2-O-CH_3. In some embodiments, R_2 is -O-R_8-O-R_{10}. In some embodiments, R_2 is O-CH_2-CH_2-O-CH_3. In some embodiments, R_2 is CN. In some embodiments, R_2 is R_8-$N(R_{10})(R_{11})$. In some embodiments, R_2 is CH_2-NH-CH_3. In some embodiments, R_2 is CH_2-NH-C(O)CH_3. In some embodiments, R_2 is CH_2-$N(CH_3)_2$). In some embodiments, R_2 is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R_2 is methyl. In other embodiments, R_2 is ethyl. In other embodiments, R_2 is iso-propyl. In other embodiments, R_2 is t-Bu. In other embodiments, R_2 is iso-butyl. In other embodiments, R_2 is pentyl. In other embodiments, R_2 is propyl. In other embodiments, R_2 is benzyl. In other embodiments, R_2 is in the ortho position. In other embodiments, R_2 is an *ortho*-methyl. In other embodiments, R_2 is C_1-C_5 linear, branched or cyclic alkoxy. In other embodiments, R_2 is methoxy. In other embodiments, R_2 is ethoxy. In other embodiments, R_2 is propoxy. In other embodiments, R_2 is isopropoxy. In other embodiments, R_2 is substituted or unsubstituted aryl. In other embodiments, R_2 is phenyl. In other embodiments, substitutions include: C_1-C_5 linear or branched alkyl (e.g. methyl), aryl, phenyl, heteroaryl (e.g., imidazole), and/or C_3-C_8 cycloalkyl, each is a separate embodiment according to this invention.

[0098] In some embodiments, **R_1** and **R_2** of formula **I** are joined together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring. In some embodiments, R_1 and R_2 are joined together to form a 5 or 6 membered heterocyclic ring. In some embodiments, R_1 and R_2 are joined together to form a pyrrol ring. In some embodiments, R_1 and R_2 are joined together to form a [1,3]dioxole ring. In some embodiments, R_1 and R_2 are joined together to form a 1,4-dioxane ring. In some embodiments, R_1 and R_2 are joined together to form a 2,3-dihydro-1,4-dioxine ring. In some embodiments, R_1 and R_2 are joined together to form a furan-2(3H)-one ring. In some embodiments, R_1 and R_2 are joined together to form a benzene ring. In some embodiments, R_1 and R_2 are joined together to form a pyridine ring. In some embodiments, R_1 and R_2 are joined together to form a morpholine ring. In some embodiments, R_1 and R_2 are joined together to form a piperazine ring.

In some embodiments, R_1 and R_2 are joined together to form an imidazole ring. In some embodiments, R_1 and R_2 are joined together to form a pyrrole ring. In some embodiments, R_1 and R_2 are joined together to form a cyclohexene ring. In some embodiments, R_1 and R_2 are joined together to form a pyrazine ring.

[0099] In various embodiments, $\mathbf{R_3}$ of formula **I-II;** and/or $\mathbf{R_4}$ of formula **I;** are each independently H. In various embodiments, $\mathbf{R_3}$ of formula **I-II;** and/or $\mathbf{R_4}$ of formula **I;** are each independently F, Cl, Br, I, OH, SH, R_8-OH, R_8-SH, -R_8-O-R_{10}, , R_8-(C_3-C_8 cycloalkyl), R_8-(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, $N(R_{10})(R_{11})$ (e.g., morpholine, piperazine, 1-(piperazin-1-yl)ethenone, 1- or 4-(methylsulfonyl)piperazine), R_8-$N(R_{10})(R_{11})$, R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, $NHC(O)$-R_{10}, $NHCO$-$N(R_{10})(R_{11})$, COOH, -C(O)Ph, $C(O)O$-R_{10}, R_8-$C(O)$-R_{10}, C(O)H, $C(O)$-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -$C(O)NH_2$, C(O)NHR, $C(O)NH(CH_3)_2O$-CH_3, $C(O)N(R_{10})(R_{11})$, C(O)-piperidine, C(O)-pyrrolidine, $C(O)N(CH_3)_2$, C(O)-piperazine, SO_2R, $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH$-$R_{10})$, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear, branched or cyclic haloalkyl, CHF_2, C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy, 1-(methylsulfonyl)piperidin-4-oxy, 1-(methyl)piperidin-4-oxy, 1-(ethanone)piperidin-4-oxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted, single, spirocyclic, fused, or bridged C_3-C_{10} heterocyclic ring (e.g., piperazine, 1-(2-methoxyethyl)piperazine, 1-, or 4-methylpiperazine, 1- or 4-(methylsulfonyl)piperazine, 1- or 4-(methylsulfonyl)piperidine, 2-methoxy-1-(piperazin-1-yl)ethenone, 1-(piperazin-1-yl)ethanone, 2-(dimethylamino)-1-(piperazin-1-yl)ethanone, 2-(dimethylamino)-1-(piperazin-1-yl)propanone, 2-hydroxy-1-(piperazin-1-yl)ethenone, *N*-methylpiperazine-1-carboxamide, piperidin-4-ol, morpholine, 3-methylmorpholine, 3-hydroxypiperidine, tetrahydro-2H-thiopyran 1,1-dioxide , tetrahydro-*2H*-pyrane, pyrazole, thiazole, imidazole, pyrrolidine, pyrrolidinone, octahydropyrrolo[1,2-α]pyrazine, 6-methyl-2,6-diazaspiro[3.3]heptane, 2-oxa-7-azaspiro[3.5]nonane, 1-(2,6-diazaspiro[3.3]heptan-2-yl)ethenone, 2-methoxy-1-(2,6-diazaspiro[3.3]heptan-2-yl)ethenone, 2,8-diazaspiro[4.5]decan-1-one, 2-oxa-7-azaspiro[3.5]nonane), substituted or unsubstituted aryl (e.g., phenyl), or substituted or unsubstituted benzyl; each possibility represents a separate embodiment of this invention. In some embodiment, R_3 and/or R_4 may be further substituted by at least one substituent selected from: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., $C(O)$-CH_3, $C(O)$-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl and (benzyloxy)phenyl; each possibility represents a separate embodiment of this invention.

[00100] In some embodiments, $\mathbf{R_3}$ of formula **I-III** is H. In other embodiments, $\mathbf{R_3}$ is F. In other embodiments, $\mathbf{R_3}$ is Cl. In other embodiments, $\mathbf{R_3}$ is Br. In other embodiments, $\mathbf{R_3}$ is I. In other embodiments, $\mathbf{R_3}$ is $N(R_{10})(R_{11})$. In other embodiments, $\mathbf{R_3}$ is $N(R_{10})(R_{11})$, wherein $N(R_{10})(R_{11})$ is a substituted or unsubstituted 3-8 membered heterocycle. In other embodiments, the heterocycle is a substituted piperazine. In other embodiments, the heterocycle is 1-(piperazin-1-yl)ethanone. In other embodiments, the heterocycle is morpholine, alkyl substituted morpholine, pyrrolidine, pyrrolidinone, piperazine, alkyl substituted piperazine (e.g., 1-(2-methoxyethyl)piperazine), amide substituted piperazine (e.g., 1- or 4-(methylsulfonyl)piperazine, *N*-methylpiperazine-1-carboxamide or 1-(piperazin-1-yl)ethanone) sulphonyl substituted piperazine (e.g., 1- or 4-(methylsulfonyl)piperazine), octahydropyrrolo[1,2-α]pyrazine, hydroxy substituted piperidine, sulphonyl substituted piperidine (e.g., 1- or 4-(methylsulfonyl)piperidine), 2-methoxy-1-(piperazin-1-yl)ethenone, tetrahydro-*2H*-pyrane, tetrahydro-2H-thiopyran 1,1-dioxide, 6-methyl-2,6-diazaspiro[3.3]heptane; each is a separate embodiment according to this invention. In other embodiments, $\mathbf{R_3}$ is morpholine. In other embodiments, $\mathbf{R_3}$ is piperazine. In other embodiments, $\mathbf{R_3}$ is substituted or unsubstituted C_3-C_8 cycloalkyl. In other embodiments, $\mathbf{R_3}$ is substituted or unsubstituted, single, spirocyclic, fused, or bridged C_3-C_{10} heterocyclic ring. In other embodiments, $\mathbf{R_3}$ is 1-(piperazin-1-yl)ethanone. In other embodiments, $\mathbf{R_3}$ is 1- or 4-(methylsulfonyl)piperazine. In some embodiments, $\mathbf{R_3}$ is a morpholine, 3-methylmorpholine, 3-hydroxypiperidine, pyrrolidine, pyrrolidinone, octahydropyrrolo[1,2-α]pyrazine, or 6-methyl-2,6-diazaspiro[3.3]heptane; each represents a separate embodiment according to this invention. In other embodiments, $\mathbf{R_3}$ may be further substituted with at least one substituent selected from: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., C(O)-CH_3, C(O)-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl and (benzyloxy)phenyl.

[00101] In some embodiments, $\mathbf{R_4}$ of formula **I** is H. In other embodiments, $\mathbf{R_4}$ is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, $\mathbf{R_4}$ is methyl. In other embodiments, $\mathbf{R_4}$ is ethyl.

[00102] In some embodiments, $\mathbf{R_3}$ and $\mathbf{R_4}$ of compound of formula **I** are joined together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring. In some embodiments, $\mathbf{R_3}$ and $\mathbf{R_4}$ are joined together to form a 5 or 6 membered carbocyclic ring. In some embodiments, R_3 and R_4 are joined together to form a 5 or 6 membered heterocyclic ring. In some embodiments, R_3 and R_4 are joined together to form a dioxole ring. [1,3]dioxole ring. In some embodiments, R_3 and R_4 are joined together to form a dihydrofuran-2(3H)-one ring. In some embodiments, R_3 and R_4 are joined together to form a furan-2(3H)-one ring. In some embodiments, R_3 and R_4 are joined together to form a benzene ring. In some embodiments, R_3 and R_4 are joined together to form an imidazole ring. In some embodiments, R_3 and R_4 are joined together to form a pyridine ring. In some embodiments, R_3 and R_4 are joined together to form a thiophene ring. In some embodiments,

R_3 and R_4 are joined together to form a furane ring. In some embodiments, R_3 and R_4 are joined together to form a pyrrole ring. In some embodiments, R_3 and R_4 are joined together to form a pyrazole ring. In some embodiments, R_3 and R_4 are joined together to form a cyclohexene ring. In some embodiments, R_3 and R_4 are joined together to form a cyclopentene ring. In some embodiments, R_4 and R_3 are joined together to form a dioxepine ring.

[00103] In some embodiments, $\mathbf{R_5}$ of formula **I** is H. In some embodiments, R_5 is $\mathbf{R_{20}}$. In some embodiments, R_5 is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In some embodiments, R_5 is methyl. In some embodiments, R_5 is ethyl. In some embodiments, R_5 is C(O)-R_{10}. In some embodiments, R_5 is SO_2R. In some embodiments, $\mathbf{R_5}$ of compound of formula **I** is $\mathbf{R_{20}}$, F, Cl, Br, I, OH, SH, R_8-OH, R_8-SH, -R_8-O-R_{10}, , R_8-(C_3-C_8 cycloalkyl), R_8-(3-8 membered heterocyclic ring), CF_3, CD_3, OCD_3, CN, NO_2, -CH_2CN, -R_8CN, NH_2, NHR, $N(R)_2$, R_8-$N(R_{10})(R_{11})$, R_9-R_8-$N(R_{10})(R_{11})$, $B(OH)_2$, -$OC(O)CF_3$, -OCH_2Ph, $NHC(O)$-R_{10}, $NHCO$-$N(R_{10})(R_{11})$, COOH, -C(O)Ph, $C(O)O$-R_{10}, R_8-$C(O)$-R_{10}, C(O)H, C(O)-R_{10}, C_1-C_5 linear or branched C(O)-haloalkyl, -$C(O)NH_2$, C(O)NHR, $C(O)N(R_{10})(R_{11})$, SO_2R, $SO_2N(R_{10})(R_{11})$, $CH(CF_3)(NH$-$R_{10})$, C_1-C_5 linear or branched, substituted or unsubstituted alkyl (e.g., methyl, ethyl), C_2-C_5 linear or branched, substituted or unsubstituted alkenyl, C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), C_1-C_5 linear, branched or cyclic alkoxy (e.g. methoxy), optionally wherein at least one methylene group (CH_2) in the alkoxy is replaced with an oxygen atom, C_1-C_5 linear or branched thioalkoxy, C_1-C_5 linear or branched haloalkoxy, C_1-C_5 linear or branched alkoxyalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl (e.g., cyclopropyl), substituted or unsubstituted 3-8 membered heterocyclic ring, substituted or unsubstituted aryl, substituted or unsubstituted benzyl; each represents a separate embodiment according to this invention. In some embodiments, R_5 may be further substituted by at least one substituent selected from: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., $C(O)$-CH_3, $C(O)$-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl and (benzyloxy)phenyl; each possibility represents a separate embodiment of this invention.

[00104] In various embodiments, **n** of compound of formula **I** is 1. In some embodiments, n is 0 or 1. In some embodiments, n is between 1 and 3. In some embodiments, n is between 1 and 4. In some embodiments, n is between 1 and 2. In some embodiments, n is between 0 and 3. In some embodiments, n is between 0 and 4. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[00105] In various embodiments, **m** of compound of formula **I** is 0. In some embodiments, m is 0 or 1. In some embodiments, m is between 1 and 3. In some embodiments, m is between 1 and 4. In some embodiments, m is between 0 and 2. In some embodiments, m is between 0 and 3. In some embodiments, m is between 0 and 4. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4.

[00106] In various embodiments, **l** of compound of formula **I** is 0. In some embodiments, l is 0 or 1. In some embodiments, l is between 1 and 3. In some embodiments, l is between 1 and 4. In some embodiments, l is 1 or 2. In some embodiments, l is between 0 and 3. In some embodiments, l is between 0 and 4. In some embodiments, l is 1. In some embodiments, l is 2. In some embodiments, l is 3. In some embodiments, l is 4.

[00107] In various embodiments, **k** of compound of formula **I** is 0. In some embodiments, k is 0 or 1. In some embodiments, k is between 1 and 3. In some embodiments, k is between 1 and 4. In some embodiments, k is between 0 and 2. In some embodiments, k is between 0 and 3. In some embodiments, k is between 0 and 4. In some embodiments, k is 1. In some embodiments, k is 2. In some embodiments, k is 3. In some embodiments, k is 4.

[00108] It is understood that for heterocyclic and/or heteroaromatic rings **A** or **B**, n, m, l and/or k are limited to the number of available positions for substitution, i.e. to the number of CH or NH groups minus one. Accordingly, if A and/or B rings are, for example, furanyl, thiophenyl or pyrrolyl, n, m, l and k are between 0 and 2; and if A and/or B rings are, for example, oxazolyl, imidazolyl or thiazolyl, n, m, l and k are either 0 or 1; and if A and/or B rings are, for example, oxadiazolyl or thiadiazolyl, n, m, l and k are 0.

[00109] In various embodiments, $\mathbf{R_6}$ of compound of formula **I-III** is absent. In various embodiments, $\mathbf{R_6}$ is CH_2. In some embodiments, R_6 is CH_2CH_2. In some embodiments, R_6 is $CH_2CH_2CH_2$. In some embodiments, R_6 is $CH_2CH_2CH_2CH_2$.

[00110] In various embodiments, **w** of compound of formula **I-V** is 0. In some embodiments, w is 1. In some embodiments, w is 2. In some embodiments, w is 3. In some embodiments, w is 4. In some embodiments, w is 5. In some embodiments, w is between 0 and 3. In some embodiments, w is between 0 and 2. In some embodiments, w is between 1 and 2. In some embodiments, w is between 0 and 4. In other embodiments, **w** is between 1 and 3. In other embodiments, **w** is 0 or 1.

[00111] In various embodiments, $\mathbf{R_8}$ of compound of formula **I-III** is CH_2. In some embodiments, R_8 is CH_2CH_2. In some embodiments, R_8 is $CH_2CH_2CH_2$. In some embodiments, R_8 is $CH_2CH_2CH_2CH_2$.

[00112] In various embodiments, **p** of compound of formula **I-V** is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is between 1 and 3. In other embodiments, **p** is 1 or 2. In some embodiments, p is between 1 and 5. In some embodiments, p is between 1 and 10.

[00113] In some embodiments, $\mathbf{R_9}$ of compound of formula **I-III** is C≡C. In some embodiments, R_9 is C≡C-C≡C. In some embodiments, R_9 is CH=CH. In some embodiments, R_9 is CH=CH-CH=CH.

[00114] In some embodiments, **q** of compound of formula **I-III** is 2. In some embodiments, q is 4. In some embodiments, q is 6. In some embodiments, q is 8. In some embodiments, q is between 2 and 6.

[00115] In various embodiments, $\mathbf{R_{10}}$ of compound of formula **I-V** is H. In some embodiments, R_{10} is OH. In some embodiments, R_{10} is substituted or unsubstituted C_1-C_5 linear or branched alkyl. In some embodiments, R_{10} is methyl. In some embodiments, R_{10} is ethyl. In some embodiments, R_{10} is propyl. In some embodiments, R_{10} is isopropyl. In some embodiments, R_{10} is butyl. In some embodiments, R_{10} is isobutyl. In some embodiments, R_{10} is t-butyl. In some embodiments, R_{10} is cyclopropyl. In some

embodiments, R_{10} is pentyl. In some embodiments, R_{10} is isopentyl. In some embodiments, R_{10} is neopentyl. In some embodiments, R_{10} is benzyl. In some embodiments, R_{10} is CH_2-CH_2-O-CH_3. In some embodiments, R_{10} is substituted or unsubstituted 3-8 membered heterocyclic ring. In some embodiments, R_{10} is tetrahydro-*2H*-pyrane. In some embodiments, R_{10} is 1-(methylsulfonyl)piperidine. In some embodiments, R_{10} is 1-(methylsulfonyl)piperazine. In some embodiments, R_{10} is morpholine. In some embodiments, R_{10} is thiomorpholine 1,1-dioxide. In some embodiments, R_{10} is methyl-pyrrolidine. In some embodiments, R_{10} is methyl-piperidine. In some embodiments, R_{10} is C(O)-alkyl. In some embodiments, R_{10} is $S(O)_2$-alkyl. In some embodiments, R_{10} may be further substituted by at least one substituent selected from: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., C(O)-CH_3, C(O)-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl and (benzyloxy)phenyl; each possibility represents a separate embodiment of this invention.

[00116] In various embodiments, $\mathbf{R_{11}}$ of compound of formula **I-V** is H. In some embodiments, R_{11} is OH. In some embodiments, R_{11} is C_1-C_5 linear or branched alkyl. In some embodiments, R_{11} is methyl. In some embodiments, R_{11} is ethyl. In some embodiments, R_{10} is propyl. In some embodiments, R_{11} is isopropyl. In some embodiments, R_{11} is butyl. In some embodiments, R_{11} is isobutyl. In some embodiments, R_{11} is t-butyl. In some embodiments, R_{11} is cyclopropyl. In some embodiments, R_{11} is pentyl. In some embodiments, R_{11} is isopentyl. In some embodiments, R_{11} is neopentyl. In some embodiments, R_{11} is benzyl. In some embodiments, R_{11} is CH_2-CH_2-O-CH_3. In some embodiments, R_{11} is substituted or unsubstituted 3-8 membered heterocyclic ring. In some embodiments, R_{11} is 1-(methylsulfonyl)piperidine. In some embodiments, R_{11} is 1-(methylsulfonyl)piperazine. In some embodiments, R_{11} is tetrahydro-*2H*-pyrane. In some embodiments, R_{11} is morpholine. In some embodiments, R_{11} is thiomorpholine 1,1-dioxide. In some embodiments, R_{11} is methyl-pyrrolidine. In some embodiments, R_{11} is methyl-piperidine. In some embodiments, R_{11} is C(O)-alkyl. In some embodiments, R_{11} is $S(O)_2$-alkyl. In some embodiments, R_{11} may be further substituted by at least one substituent selected from: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., C(O)-CH_3, C(O)-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl and (benzyloxy)phenyl; each possibility represents a separate embodiment of this invention.

[00117] In some embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ of formula **I-V** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a morpholine ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a piperazine ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a substituted piperazine ring. In other embodiments, $\mathbf{R_{10}}$

and $\mathbf{R_{11}}$ are joined to form a 1-(piperazin-1-yl)ethenone. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a 1- or 4-(methylsulfonyl)piperazine. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a piperidine ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form an unsubstituted pyrrolidine ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a 1-methylpyrrolidin-2-one ring. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form an oxetane. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form an azetidine. In other embodiments, $\mathbf{R_{10}}$ and $\mathbf{R_{11}}$ are joined to form a 1-methylazetidine. In some embodiments, R_{10} and/or R_{11} may be further substituted by at least one substituent selected from: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., C(O)-CH_3, C(O)-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl and (benzyloxy)phenyl; each possibility represents a separate embodiment of this invention..

[00118] In some embodiments, $\mathbf{R_{12}}$ of formula **IV** is H. In some embodiments, R_{12} is substituted or unsubstituted C_1-C_5 linear or branched alkyl. In some embodiments, $\mathbf{R_{12}}$ is a C_1-C_5 linear alkyl. In some embodiments, $\mathbf{R_{12}}$ is C_1-C_5 branched alkyl. In some embodiments, R_{12} is methyl. In some embodiments, R_{12} is ethyl. In some embodiments, R_{12} is propyl. In some embodiments, R_{12} is isopropyl. In some embodiments, R_{12} is butyl. In some embodiments, R_{12} is isobutyl. In some embodiments, R_{12} is t-butyl. In some embodiments, R_{12} is cyclopropyl. In some embodiments, R_{12} is pentyl. In some embodiments, R_{12} is isopentyl. In some embodiments, R_{12} is neopentyl. In some embodiments, R_{12} is CH_2-CH_2-O-CH_3. In some embodiments, R_{12} may be further substituted by at least one substituent selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, OH, C_1-C_5 linear or branched alkoxy, cyclic alkoxy, amide (i.e., C(O)-NH-alkyl or NH-C(O)-alkyl), $C(O)N(R_{10})(R_{11})$, amine (i.e., $NH(R_{10})$, $N(R_{10})(R_{11})$, NH_2), aryl, phenyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted 3-8 membered heterocyclic ring, which may be saturated, unsaturated, aromatic, single, fused, bridged or spiral; each represents a separate embodiment according to this invention. In some embodiments, $\mathbf{R_{12}}$ is unsubstituted.

[00119] In some embodiments, $\mathbf{R_{30}}$ of formula **I-V** is substituted or unsubstituted C_1-C_5 linear or branched alkyl. In some embodiments, the alkyl may be further substituted with at least one selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, C_1-C_5 linear or branched alkoxy (e.g. OCH_3), C_2-C_5 linear or branched alkynyl (e.g. CCH), C_1-C_5 linear or branched thioalkoxy (e.g. SCH_3), C_1-C_5 linear or branched alkylsulfinyl (e.g. $S(O)CH_3$), C_1-C_5 linear or branched alkylsulfonyl (e.g. $S(O)_2$-CH_3), NH_2, C_1-C_5 linear or branched N(H)(alkyl) (e.g., $N(H)(CH_3)$), and C_1-C_5 linear or branched $N(alkyl)_2$; each represents a separate embodiment according to this invention. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is $C(H)(OH)(CH_3)$. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is methyl. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is ethyl. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-O-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-O-CH_3. In some embodiments, the substituted or

unsubstituted C_1-C_5 linear or branched alkyl is CH_2-S-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-S-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-S(O)-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-S(O)-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-$S(O)_2$-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-$S(O)_2$-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-NH-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CH_2-NH-CH_3. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CCH. In some embodiments, the substituted or unsubstituted C_1-C_5 linear or branched alkyl is CH_2-CHF_2. In some embodiments, $\mathbf{R_{30}}$ is C_2-C_5 linear or branched, substituted or unsubstituted alkynyl. In some embodiments, the C_2-C_5 linear or branched, substituted or unsubstituted alkynyl is CCH. In some embodiments, $\mathbf{R_{30}}$ is C_1-C_5 linear or branched alkoxy. In some embodiments, the C_1-C_5 linear or branched alkoxy is O-CH_3. In some embodiments, $\mathbf{R_{30}}$ is C_1-C_5 linear or branched thioalkoxy. In some embodiments, the C_1-C_5 linear or branched thioalkoxy is S-CH_3. In some embodiments, $\mathbf{R_{30}}$ is C_1-C_5 linear, branched or cyclic haloalkyl. In some embodiments, the C_1-C_5 linear, branched or cyclic haloalkyl is CHF_2. In some embodiments, $\mathbf{R_{30}}$ is substituted or unsubstituted 3-8 membered heterocyclic ring. In some embodiments, the substituted or unsubstituted 3-8 membered heterocyclic ring is tetrahydro-*2H*-pyrane. In some embodiments, $\mathbf{R_{30}}$ is $N(R_{10})(R_{11})$. In some embodiments, $N(R_{10})(R_{11})$ is N(H)(CH_3). In some embodiments, $\mathbf{R_{30}}$ is S(O)R. In some embodiments, S(O)R is S(O)-CH_3. In some embodiments, $\mathbf{R_{30}}$ is SO_2R. In some embodiments, SO_2R is SO_2-CH_3.

[00120] In some embodiments, **R** of formula **I-V** is H. In other embodiments, R is OH. In other embodiments, R is F. In other embodiments, R is Cl. In other embodiments, R is Br. In other embodiments, R is I. In other embodiments, R is CN. In other embodiments, R is CF_3. In other embodiments, R is NO_2. In other embodiments, R is NH_2. In other embodiments, R is $NH(R_{10})$. In other embodiments, R is NH(CH_3). In other embodiments, R is $N(R_{10})(R_{11})$. In other embodiments, R is R_{20}. In other embodiments, R is C_1-C_5 linear or branched, substituted or unsubstituted alkyl. In other embodiments, R is methyl. In other embodiments, R is ethyl. In other embodiments, R is substituted alkyl. In other embodiments, R is CH_2CH_2OH. In other embodiments, R is $CH_2CH_2OCH_3$. In other embodiments, R is R_8-R_{10}. In other embodiments, R is CH_2-OH. In other embodiments, R is CH_2CH_2-OH. In other embodiments, R is C(O)-R_{10}. In other embodiments, R is C(O)-methylpyrroldine. In other embodiments, R is C(O)-methylpiperidine. In other embodiments, R is C(O)-CH_3. In other embodiments, R is -R_8-O-R_{10}. In other embodiments, R is CH_2-CH_2-O-CH_3. In other embodiments, R is C_1-C_5 substituted or unsubstituted C(O)-alkyl. In other embodiments, R is C(O)-CH_2CH_2-OCH_3. In other embodiments, R is C(O)-CH_3. In other embodiments, R is C(O)-CH_2-$N(CH_3)_2$. In other embodiments, R is C(O)-CH_2-CH_2-$N(CH_3)_2$. In other embodiments, R is C(O)-CH_2-OH. In other embodiments, R is C(O)-R_8-R_{10}. In other embodiments, R is C(O)-CH_2CH_2-OH. In other embodiments, R is C(O)-substituted or unsubstituted 3-8 membered heterocyclic ring. In other embodiments, R is C(O)-methylpyrroldine. In other embodiments, R is C(O)-methylpiperidine. In other embodiments, R is

SO_2-alkyl. In other embodiments, R is SO_2-CH_3. In other embodiments, R is C_1-C_5 substituted or unsubstituted C(O)-NH-alkyl. In other embodiments, R is C(O)-NH-CH_3. In other embodiments, R is C_1-C_5 linear or branched C(O)-O-alkyl. In other embodiments, R is C(O)-O-tBu. In other embodiments, R is C_1-C_5 linear or branched alkoxy. In other embodiments, R is -R_8-O-R_{10}. In other embodiments, R is CH_2-CH_2-O-CH_3. In other embodiments, R is C_1-C_5 linear or branched haloalkyl. In other embodiments, R is CF_3. In other embodiments, R is CF_2CH_3. In other embodiments, R is CH_2CF_3. In other embodiments, R is $CF_2CH_2CH_3$. In other embodiments, R is $CH_2CH_2CF_3$. In other embodiments, R is $CF_2CH(CH_3)_2$. In other embodiments, R is $CF(CH_3)$-$CH(CH_3)_2$. In other embodiments, R is R_8-aryl. In other embodiments, R is CH_2-Ph. In other embodiments, R is substituted or unsubstituted aryl. In other embodiments, R is phenyl. In other embodiments, R is substituted or unsubstituted heteroaryl. In other embodiments, R is pyridine. In other embodiments, R is 2, 3, or 4-pyridine. In some embodiments, R may be further substituted by at least one substituent selected from: F, Cl, Br, I, OH, SH, CF_3, CN, NO_2, substituted or unsubstituted C_1-C_5 linear or branched alkyl (e.g., methyl, methoxyethyl), substituted or unsubstituted C_1-C_5 linear or branched C(O)-alkyl (e.g., C(O)-CH_3, C(O)-CH_2-O-CH_3), SO_2-alkyl (e.g., SO_2-CH_3), C(O)-NH-alkyl, C_1-C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2$-OH, CH_2CH_2-OH), 3-8 membered heterocyclic ring (e.g., piperidine), substituted or unsubstituted C_1-C_5 linear or branched alkoxy, $N(R)_2$, $N(R_{10})(R_{11})$, aryl, phenyl, heteroaryl, C_3-C_8 cycloalkyl, halophenyl and (benzyloxy)phenyl; each possibility represents a separate embodiment of this invention.. In some embodiment, two geminal **R** substitutions are joined together to form a 3 - 6 membered substituted or unsubstituted, aliphatic (e.g., cyclopropyl, cyclopentene) or aromatic, carbocyclic (e.g., benzene) or heterocyclic (e.g., thiophene, furane, pyrrol, pyrazole) ring; each represents a separate embodiment according to this invention.

[00121] It is understood that H atoms are added where necessary, in order to complete the valence of the unsubstituted carbon atoms of $\mathbf{X_1}$-$\mathbf{X_5}$ of any one of formulas **II**-**V**.

[00122] In some embodiments, $\mathbf{X_6}$ of compound of formula **III** is O. In other embodiments, $\mathbf{X_6}$ is CH_2. In other embodiments, $\mathbf{X_6}$ is CHR. In other embodiments, $\mathbf{X_6}$ is CH(OH). In other embodiments, $\mathbf{X_6}$ is $CH(NH_2)$. In other embodiments, $\mathbf{X_6}$ is $CH(NH(CH_3))$. In other embodiments, $\mathbf{X_6}$ is $C(R_{10})(R_{11})$. In other embodiments, $\mathbf{X_6}$ is C(H)CH_2CH_2-OH. In other embodiments, $\mathbf{X_6}$ is C(H)CH_2-OH. In other embodiments, $\mathbf{X_6}$ is 1-methylpyrrolidin-2-one. In other embodiments, $\mathbf{X_6}$ is oxetane. In other embodiments, $\mathbf{X_6}$ is NH. In other embodiments, $\mathbf{X_6}$ is N-R. In other embodiments, $\mathbf{X_6}$ is N-CH_3. In other embodiments, $\mathbf{X_6}$ is N-SO_2-CH_3. In other embodiments, $\mathbf{X_6}$ is N-$S(O)_2$-R_{10}. In other embodiments, $\mathbf{X_6}$ is N-R_{20}. In other embodiments, $\mathbf{X_6}$ is N-C(O)O-tBu. In other embodiments, $\mathbf{X_6}$ is N-C(O)-CH_2CH_2-OCH_3. In other embodiments, $\mathbf{X_6}$ is N-CH_2CH_2-OCH_3. In other embodiments, $\mathbf{X_6}$ is N-C(O)-CH_3. In other embodiments, $\mathbf{X_6}$ is C_1-C_5 substitued or unsubstituted N-C(O)-NH-alkyl. In other embodiments, $\mathbf{X_6}$ is N-C(O)-NH-CH_3. In other embodiments, $\mathbf{X_6}$ is N-C(O)-CH_2-$N(CH_3)_2$. In other embodiments, $\mathbf{X_6}$ is N-C(O)-CH_2-CH_2-$N(CH_3)_2$. In other embodiments, $\mathbf{X_6}$ is N-C(O)-CH_2CH_2-OH. In other embodiments, $\mathbf{X_6}$ is N-C(O)-CH_2-OH. In other embodiments, $\mathbf{X_6}$ is N-C(O)-R_{10}. In other embodiments, $\mathbf{X_6}$ is 1-methylazetidine. In other embodiments, $\mathbf{X_6}$ is N-C(O)-1-methyl-2-pyrrolidine. In other embodiments, $\mathbf{X_6}$ is N-C(O)-1-methyl-3-pyrrolidine. In other embodiments, $\mathbf{X_6}$ is N-C(O)-1-methyl-3-

piperidine. In other embodiments, $\mathbf{X_6}$ is N-C(O)-1-methyl-4-piperidine. In other embodiments, $\mathbf{X_6}$ is N-R_{20}.

[00123] In some embodiments, at least one of $\mathbf{X_1}$-$\mathbf{X_2}$ of formula **II-III** is N.

[00124] In some embodiments, at least one of $\mathbf{X_3}$-$\mathbf{X_5}$ of formula **II-III** is N. In some embodiments, at least two of $\mathbf{X_3}$-$\mathbf{X_5}$ are N. In some embodiments, $\mathbf{X_3}$ is N.

[00125] In some embodiments, $\mathbf{Q_1}$ of formula **I** is S. In other embodiments, $\mathbf{Q_1}$ is O. In other embodiments, $\mathbf{Q_1}$ is NH.

[00126] In some embodiments, **G=X** of formula **I** is C=O. In other embodiments, **G=X** is C=S. In other embodiments, **G=X** is S=O. In other embodiments, **G=X** is SO_2.

[00127] In some embodiments, **G'=X'** of compound of formula **IV** is C=O. In some embodiments, **G'=X'** is $S(O)_2$. In some embodiments, **G'=X'** is S(O).

[00128] As used herein, "single or fused aromatic or heteroaromatic ring systems" can be any such ring, including but not limited to phenyl, naphthyl, pyridinyl, (2-, 3-, and 4-pyridinyl), quinolinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, 1-methylimidazole, pyrazolyl, pyrrolyl, furanyl, thiophene-yl, quinolinyl, isoquinolinyl, 2,3-dihydroindenyl, indenyl, tetrahydronaphthyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepine , benzodioxolyl, benzo[d][1,3]dioxole, tetrahydronaphthyl, indolyl, 1H-indole, isoindolyl, anthracenyl, benzimidazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, indazolyl, 2H-indazole, triazolyl, 4,5,6,7-tetrahydro-2H-indazole, 3H-indol-3-one, purinyl, benzoxazolyl, 1,3-benzoxazolyl, benzisoxazolyl, benzothiazolyl, 1,3-benzothiazole, 4,5,6,7-tetrahydro-1,3-benzothiazole, quinazolinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinoxaline, 1-(pyridin-1(2H)-yl)ethanone, cinnolinyl, phthalazinyl, quinolinyl, isoquinolinyl, acridinyl, benzofuranyl, 1-benzofuran, isobenzofuranyl, benzofuran-2(3H)-one, benzothiophenyl, benzoxadiazole, benzo[c][1,2,5]oxadiazolyl, benzo[*c*]thiophenyl, benzodioxolyl, thiadiazolyl, [1,3]oxazolo[4,5-b]pyridine, oxadiaziolyl, imidazo[2,1-b][1,3]thiazole, 4H,5H,6H-cyclopenta[d][1,3]thiazole, 5H,6H,7H,8H-imidazo[1,2-a]pyridine, 7-oxo-6H,7H-[1,3]thiazolo[4,5-d]pyrimidine, [1,3]thiazolo[5,4-b]pyridine, 2H,3H-imidazo[2,1-b][1,3]thiazole, thieno[3,2-d]pyrimidin-4(3H)-one, 4-oxo-4H-thieno[3,2-d][1,3]thiazin, imidazo[1,2-a]pyridine, 1H-imidazo[4,5-b]pyridine, 1H-imidazo[4,5-c]pyridine, 3H-imidazo[4,5-c]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, 1H-pyrrolo[2,3-b]pyridine, pyrido[2,3-b]pyrazine, pyrido[2,3-b]pyrazin-3(4H)-one, 4H-thieno[3,2-b]pyrrole, quinoxalin-2(1H)-one, 1H-pyrrolo[3,2-b]pyridine, 7H-pyrrolo[2,3-d]pyrimidine, oxazolo[5,4-b]pyridine, thiazolo[5,4-b]pyridine, thieno[3,2-c]pyridine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, etc.

[00129] As used herein, the term "alkyl" can be any straight- or branched-chain alkyl group containing up to about 30 carbons unless otherwise specified. In various embodiments, an alkyl includes C_1-C_5 carbons. In some embodiments, an alkyl includes C_1-C_6 carbons. In some embodiments, an alkyl includes C_1-C_8 carbons. In some embodiments, an alkyl includes C_1-C_{10} carbons. In some embodiments, an alkyl is a C_1-C_{12} carbons. In some embodiments, an alkyl is a C_1-C_{20} carbons. In some embodiments, branched alkyl is an alkyl substituted by alkyl side chains of 1 to 5 carbons. In various embodiments,

the alkyl group may be unsubstituted. In some embodiments, the alkyl group may be substituted by a halogen, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO_2H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C_1-C_5 linear or branched haloalkoxy, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, -CH_2CN, NH_2, NH-alkyl, N(alkyl)$_2$, -OC(O)CF_3, -OCH_2Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH_2 or any combination thereof.

[00130] The alkyl group can be a sole substituent, or it can be a component of a larger substituent, such as in an alkoxy, alkoxyalkyl, haloalkyl, arylalkyl, alkylamino, dialkylamino, alkylamido, alkylurea, etc. Preferred alkyl groups are methyl, ethyl, and propyl, and thus halomethyl, dihalomethyl, trihalomethyl, haloethyl, dihaloethyl, trihaloethyl, halopropyl, dihalopropyl, trihalopropyl, methoxy, ethoxy, propoxy, arylmethyl, arylethyl, arylpropyl, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, methylamido, acetamido, propylamido, halomethylamido, haloethylamido, halopropylamido, methyl-urea, ethyl-urea, propyl-urea, 2, 3, or 4-CH_2-C_6H_4-Cl, C(OH)(CH_3)(Ph), etc.

[00131] As used herein, the term "aryl" refers to any aromatic ring that is directly bonded to another group and can be either substituted or unsubstituted. The aryl group can be a sole substituent, or the aryl group can be a component of a larger substituent, such as in an arylalkyl, arylamino, arylamido, etc. Exemplary aryl groups include, without limitation, phenyl, tolyl, xylyl, furanyl, naphthyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, thiazolyl, oxazolyl, isooxazolyl, pyrazolyl, imidazolyl, thiophene-yl, pyrrolyl, indolyl, phenylmethyl, phenylethyl, phenylamino, phenylamido, 3-methyl-4H-1,2,4-triazolyl, 5-methyl-1,2,4-oxadiazolyl, etc. Substitutions include but are not limited to: F, Cl, Br, I, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 linear or branched alkoxy, C_1-C_5 linear or branched haloalkoxy, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO_2, -CH_2CN, NH_2, NH-alkyl, N(alkyl)$_2$, hydroxyl, -OC(O)CF_3, -OCH_2Ph, -NHCO-alkyl, COOH, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH_2 or any combination thereof.

[00132] As used herein, the term "alkoxy" refers to an ether group substituted by an alkyl group as defined above. Alkoxy refers both to linear and to branched alkoxy groups. Nonlimiting examples of alkoxy groups are methoxy, ethoxy, propoxy, *iso*-propoxy, *tert*-butoxy.

[00133] As used herein, the term "aminoalkyl" refers to an amine group substituted by an alkyl group as defined above. Aminoalkyl refers to monoalkylamine, dialkylamine or trialkylamine. Nonlimiting examples of aminoalkyl groups are -N(Me)$_2$, -NHMe, -NH_3.

[00134] A "haloalkyl" group refers, in some embodiments, to an alkyl group as defined above, which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I. The term "haloalkyl" include but is not limited to fluoroalkyl, i.e., to an alkyl group bearing at least one fluorine atom. Nonlimiting examples of haloalkyl groups are CF_3, CF_2CF_3, CF_2CH_3, CH_2CF_3, $CF_2CH_2CH_3$, $CH_2CH_2CF_3$, $CF_2CH(CH_3)_2$ and $CF(CH_3)$-$CH(CH_3)_2$.

[00135] A "halophenyl" group refers, in some embodiments, to a phenyl substitutent which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I. In one embodiment, the halophenyl is 4-chlorophenyl.

[00136] An "alkoxyalkyl" group refers, in some embodiments, to an alkyl group as defined above, which is substituted by alkoxy group as defined above, e.g. by methoxy, ethoxy, propoxy, i-propoxy, t-

butoxy etc. Nonlimiting examples of alkoxyalkyl groups are -CH_2-O-CH_3, -CH_2-O-$CH(CH_3)_2$, -CH_2-O-$C(CH_3)_3$, -CH_2-CH_2-O-CH_3, -CH_2-CH_2-O-$CH(CH_3)_2$, -CH_2-CH_2-O-$C(CH_3)_3$.

[00137] A "cycloalkyl" or "carbocyclic" group refers, in various embodiments, to a ring structure comprising carbon atoms as ring atoms, which may be either saturated or unsaturated, substituted or unsubstituted, single or fused. In some embodiments the cycloalkyl is a 3-10 membered ring. In some embodiments the cycloalkyl is a 3-12 membered ring. In some embodiments the cycloalkyl is a 6 membered ring. In some embodiments the cycloalkyl is a 5-7 membered ring. In some embodiments the cycloalkyl is a 3-8 membered ring. In some embodiments, the cycloalkyl group may be unsubstituted or substituted by a halogen, alkyl, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO_2H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C_1-C_5 linear or branched haloalkoxy, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, -CH_2CN, NH_2, NH-alkyl, N(alkyl)$_2$, -OC(O)CF_3, -OCH_2Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH_2 or any combination thereof. In some embodiments, the cycloalkyl ring may be fused to another saturated or unsaturated cycloalkyl or heterocyclic 3-8 membered ring. In some embodiments, the cycloalkyl ring is a saturated ring. In some embodiments, the cycloalkyl ring is an unsaturated ring. Non limiting examples of a cycloalkyl group comprise cyclohexyl, cyclohexenyl, cyclopropyl, cyclopropenyl, cyclopentyl, cyclopentenyl, cyclobutyl, cyclobutenyl, cycloctyl, cycloctadienyl (COD), cycloctaene (COE) etc.

[00138] A "heterocycle" or "heterocyclic" group refers, in various embodiments, to a ring structure comprising in addition to carbon atoms, sulfur, oxygen, nitrogen or any combination thereof, as part of the ring. A "heteroaromatic ring" refers in various embodiments, to an aromatic ring structure comprising in addition to carbon atoms, sulfur, oxygen, nitrogen or any combination thereof, as part of the ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-10 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-12 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 6 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 5-7 membered ring. In some embodiments the heterocycle or heteroaromatic ring is a 3-8 membered ring. In some embodiments, the heterocycle group or heteroaromatic ring may be unsubstituted or substituted by a halogen, alkyl, haloalkyl, hydroxyl, alkoxy, carbonyl, amido, alkylamido, dialkylamido, cyano, nitro, CO_2H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C_1-C_5 linear or branched haloalkoxy, CF_3, phenyl, halophenyl, (benzyloxy)phenyl, -CH_2CN, NH_2, NH-alkyl, N(alkyl)$_2$, -OC(O)CF_3, -OCH_2Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH_2 or any combination thereof. In some embodiments, the heterocycle ring or heteroaromatic ring may be fused to another saturated or unsaturated cycloalkyl or heterocyclic 3-8 membered ring. In some embodiments, the heterocyclic ring is a saturated ring. In some embodiments, the heterocyclic ring is an unsaturated ring. Non limiting examples of a heterocyclic ring or heteroaromatic ring systems comprise pyridine, piperidine, morpholine, piperazine, thiophene, pyrrole, benzodioxole, benzofuran-2(3H)-one, benzo[d][1,3]dioxole, indole, oxazole, isoxazole, imidazole and 1-methylimidazole, furane, triazole, pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), naphthalene, tetrahydrothiophene 1,1-dioxide, thiazole, benzimidazole, piperidine, 1-methylpiperidine, isoquinoline, 1,3-dihydroisobenzofuran, benzofuran, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, or indole.

[00139] In various embodiments, this invention provides a compound of this invention or its isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (deuterated analog), PROTAC, polymorph, or crystal or combinations thereof. In various embodiments, this invention provides an isomer of the compound of this invention. In some embodiments, this invention provides a metabolite of the compound of this invention. In some embodiments, this invention provides a pharmaceutically acceptable salt of the compound of this invention. In some embodiments, this invention provides a pharmaceutical product of the compound of this invention. In some embodiments, this invention provides a tautomer of the compound of this invention. In some embodiments, this invention provides a hydrate of the compound of this invention. In some embodiments, this invention provides an *N*-oxide of the compound of this invention. In some embodiments, this invention provides a reverse amide analog of the compound of this invention. In some embodiments, this invention provides a prodrug of the compound of this invention. In some embodiments, this invention provides an isotopic variant (including but not limited to deuterated analog) of the compound of this invention. In some embodiments, this invention provides a PROTAC (Proteolysis targeting chimera) of the compound of this invention. In some embodiments, this invention provides a polymorph of the compound of this invention. In some embodiments, this invention provides a crystal of the compound of this invention. In some embodiments, this invention provides composition comprising a compound of this invention, as described herein, or, In some embodiments, a combination of an isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (deuterated analog), PROTAC, polymorph, or crystal of the compound of this invention.

[00140] In various embodiments, the term "isomer" includes, but is not limited to, stereoisomers and analogs, structural isomers and analogs, conformational isomers and analogs, and the like. In some embodiments, the isomer is an optical isomer. In some embodiments, the isomer is a stereoisomer.

[00141] In various embodiments, this invention encompasses the use of various stereoisomers of the compounds of the invention. It will be appreciated by those skilled in the art that the compounds of the present invention may contain at least one chiral center. Accordingly, the compounds used in the methods of the present invention may exist in, and be isolated in, optically-active or racemic forms. Accordingly, the compounds according to this invention may exist as optically-active isomers (enantiomers or diastereomers, including but not limited to: the *(R)*, *(S)*, *(R)(R)*, *(R)(S)*, *(S)(S)*, *(S)(R)*, *(R)(R)(R)*, *(R)(R)(S)*, *(R)(S)(R)*, *(S)(R)(R)*, *(R)(S)(S)*, *(S)(R)(S)*, *(S)(S)(R)* or *(S)(S)(S)* isomers); as racemic mixtures, or as enantiomerically enriched mixtures. Some compounds may also exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-

active, polymorphic, or stereroisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of the various conditions described herein.

[00142] It is 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).

[00143] The compounds of the present invention can also be present in the form of a racemic mixture, containing substantially equivalent amounts of stereoisomers. In some embodiments, the compounds of the present invention can be prepared or otherwise isolated, using known procedures, to obtain a stereoisomer substantially free of its corresponding stereoisomer (i.e., substantially pure). By substantially pure, it is intended that a stereoisomer is at least about 95% pure, more preferably at least about 98% pure, most preferably at least about 99% pure. In various embodiments, the compound according to the invention comprises a substantially pure stereoisomer. In some embodiments, the substantially pure stereoisomer is at least 70%; 75%; 80%; 85%; 90%; 93%; 95%; 97%; 98%; 99%; 99.5% pure; each represents a separate embodiment according to this invention.

[00144] In various embodiments, the compound comprises a single stereoisomer in a purity of >80%; >85%; >90%; >91%; >92%; >93%; >94%; >95%; >96%; >97%; >98%; >99%; >99.5% enantiomeric excess (*ee)*; each represents a separate embodiment according to this invention. In various embodiments, the compound comprises a single stereoisomer in a purity >80%; >85%; >90%; >91%; >92%; >93%; >94%; >95%; >96%; >97%; >98%; >99%; >99.5% enantiomeric ratio (*er)*; each represents a separate embodiment according to this invention. In various embodiments, the compound comprises a single stereoisomer in a purity higher than 80%; 85%; 90%; 91%; 92%; 93%; 94%; 95%; 96%; 97%; 98%; 99%; 99.5%; each represents a separate embodiment according to this invention.

[00145] In various embodiments, the compound is a substantially pure single enantiomer. In various embodiments, the compound comprises a mixture of enantiomers. In various embodiments, the compound is a racemate.

[00146] In various embodiments, the compound has two chiral centers. In various embodiments, the compound comprises a mixture of stereoisomers. In various embodiments, the compound comprises a mixture of 2, 3, or 4 stereoisomers; each represents a separate embodiment according to this invention. In various embodiments, the compound is a single stereoisomer. In various embodiments, the compound is a substantially pure single stereoisomer. In various embodiments, the substantially pure stereoisomer has at least 80%, 85%, 90%, 95%, 97%, 98%, 99% purity; each represents a separate embodiment according to this invention. In various embodiments, the compound is the substantially pure ***RR*** stereoisomer. In various embodiments, the compound is the substantially pure ***SS*** stereoisomer. In various embodiments, the compound is the substantially pure ***RS*** stereoisomer. In various embodiments, the compound is the substantially pure ***SR*** stereoisomer.

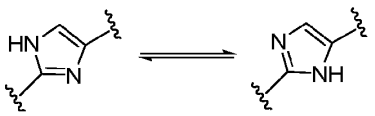
[00147] Compounds of the present invention can also be in the form of a hydrate, which means that the compound further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[00148] As used herein, a "reverse amide analog" refers to a compound in which the positions of the carbonyl group (C=O) and the amine group (-NH or -NR) in a parent amide functional group (-C(=O)-NR-) are reversed. Specifically, the reverse amide analog contains a structure of the form -NR-C(=O)-, wherein the nitrogen atom is directly bonded to the carbon atom of the carbonyl group. In some embodiments, the reverse amide analog does not consist of cyclic amides or amides of cyclic amines.

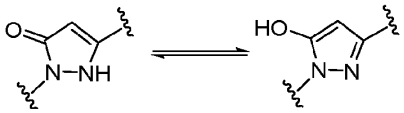
[00149] As used herein, when some chemical functional group (e.g., alkyl or aryl) is said to be "substituted", it is herein defined that one or more substitutions are possible. In some embodiments, the term "substituted" according to this invention, refers to but is not limited to at least one group selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, tertbutyl, pentyl, isopentyl, neopentyl, hexyl), C_1-C_5 linear or branched haloalkyl, OH, C_1-C_5 linear or branched alkoxy (e.g. OCH_3), cyclic alkoxy (e.g., oxetane), C_1-C_5 linear or branched thioalkoxy (e.g. SCH_3), C_1-C_5 linear or branched alkylsulfinyl (e.g. $S(O)CH_3$), C_1-C_5 linear or branched alkylsulfonyl (e.g. $S(O)_2$-CH_3), R_8-OH (e.g., CH_2-OH), OMe, amide (i.e., C(O)-NH-alkyl or NH-C(O)-alkyl), $C(O)N(R_{10})(R_{11})$, R_8-$C(O)N(R_{10})(R_{11})$, $NH(R_{10})$, $N(R_{10})(R_{11})$, NH_2, C_1-C_5 linear or branched N(H)(alkyl) (e.g., $N(H)(CH_3)$), C_1-C_5 linear or branched $N(alkyl)_2$, aryl, phenyl, heteroaryl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted 3-8 membered heterocyclic ring, which may be saturated, unsaturated, aromatic, single, fused, bridged or spiral (e.g. pyran, oxetane, piperidine, pyrazole, methyl-pyrrazole, triazole, imidazole); each represents a separate embodiment according to this invention. In some embodiments, the term "substituted" according to this invention refers to at least one group selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, C_1-C_5 linear or branched alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, tertbutyl, pentyl, isopentyl, neopentyl, hexyl), C_1-C_5 linear or branched alkoxy (e.g. OCH_3), C_2-C_5 linear or branched alkynyl (e.g. CCH), C_1-C_5 linear or branched thioalkoxy (e.g. SCH_3), C_1-C_5 linear or branched alkylsulfinyl (e.g. $S(O)CH_3$), C_1-C_5 linear or branched alkylsulfonyl (e.g. $S(O)_2$-CH_3), NH_2, C_1-C_5 linear or branched N(H)(alkyl) (e.g., $N(H)(CH_3)$), and C_1-C_5 linear or branched $N(alkyl)_2$; each represents a separate embodiment according to this invention. In some embodiments, substitutions include at least one group selected from: F, Cl, Br, I, OH, CF_3, CN, NO_2, C_1-C_5 linear or branched alkoxy (e.g. OCH_3), C_2-C_5 linear or branched alkynyl (e.g. CCH), C_1-C_5 linear or branched thioalkoxy (e.g. SCH_3), C_1-C_5 linear or branched alkylsulfinyl (e.g. $S(O)CH_3$), C_1-C_5 linear or branched alkylsulfonyl (e.g. $S(O)_2$-CH_3), C_1-C_5 linear or branched N(H)(alkyl) (e.g., $N(H)(CH_3)$) and C_1-C_5 linear or branched $N(alkyl)_2$; each represents a separate embodiment according to this invention.

[00150] Compounds of the present invention may exist in the form of one or more of the possible tautomers and depending on the conditions it may be possible to separate some or all of the tautomers into individual and distinct entities. It is to be understood that all of the possible tautomers, including all additional enol and keto tautomers and/or isomers are hereby covered. For example, the following tautomers, but not limited to these, are included:

Tautomerization of the imidazole ring:



Tautomerization of the pyrazolone ring:



[00151] The invention includes "pharmaceutically acceptable salts" of the compounds of this invention, which may be produced, by reaction of a compound of this invention with an acid or base. Certain compounds, particularly those possessing acid or basic groups, can also be in the form of a salt, preferably a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to those salts that retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxylic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, *N*-acetylcysteine and the like. Other salts are known to those of skill in the art and can readily be adapted for use in accordance with the present invention.

[00152] Suitable pharmaceutically acceptable salts of amines of compounds the compounds of this invention may be prepared from an inorganic acid or from an organic acid. In various embodiments, examples of inorganic salts of amines are bisulfates, borates, bromides, chlorides, hemisulfates, hydrobromates, hydrochlorates, 2-hydroxyethylsulfonates (hydroxyethanesulfonates), iodates, iodides, isothionates, nitrates, persulfates, phosphate, sulfates, sulfamates, sulfanilates, sulfonic acids (alkylsulfonates, arylsulfonates, halogen substituted alkylsulfonates, halogen substituted arylsulfonates), sulfonates and thiocyanates.

[00153] In various embodiments, examples of organic salts of amines may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are acetates, arginines, aspartates, ascorbates, adipates, anthranilates, algenates, alkane carboxylates, substituted alkane carboxylates, alginates, benzenesulfonates, benzoates, bisulfates, butyrates, bicarbonates, bitartrates, citrates, camphorates, camphorsulfonates, cyclohexylsulfamates, cyclopentanepropionates, calcium edetates, camsylates, carbonates, clavulanates, cinnamates, dicarboxylates, digluconates, dodecylsulfonates, dihydrochlorides, decanoates, enanthuates, ethanesulfonates, edetates, edisylates, estolates, esylates, fumarates, formates, fluorides, galacturonates gluconates, glutamates, glycolates, glucorate, glucoheptanoates, glycerophosphates, gluceptates, glycollylarsanilates, glutarates, glutamate, heptanoates, hexanoates, hydroxymaleates, hydroxycarboxlic acids, hexylresorcinates, hydroxybenzoates, hydroxynaphthoates, hydrofluorates, lactates, lactobionates, laurates, malates, maleates, methylenebis(beta-oxynaphthoate), malonates, mandelates, mesylates, methane sulfonates, methylbromides, methylnitrates, methylsulfonates,

monopotassium maleates, mucates, monocarboxylates, naphthalenesulfonates, 2-naphthalenesulfonates, nicotinates, nitrates, napsylates, *N*-methylglucamines, oxalates, octanoates, oleates, pamoates, phenylacetates, picrates, phenylbenzoates, pivalates, propionates, phthalates, phenylacetate, pectinates, phenylpropionates, palmitates, pantothenates, polygalacturates, pyruvates, quinates, salicylates, succinates, stearates, sulfanilate, subacetates, tartrates, theophyllineacetates, *p*-toluenesulfonates (tosylates), trifluoroacetates, terephthalates, tannates, teoclates, trihaloacetates, triethiodide, tricarboxylates, undecanoates and valerates.

[00154] In various embodiments, examples of inorganic salts of carboxylic acids or hydroxyls may be selected from ammonium, alkali metals to include lithium, sodium, potassium, cesium; alkaline earth metals to include calcium, magnesium, aluminium; zinc, barium, cholines, quaternary ammoniums.

[00155] In some embodiments, examples of organic salts of carboxylic acids or hydroxyl may be selected from arginine, organic amines to include aliphatic organic amines, alicyclic organic amines, aromatic organic amines, benzathines, *t*-butylamines, benethamines (*N*-benzylphenethylamine), dicyclohexylamines, dimethylamines, diethanolamines, ethanolamines, ethylenediamines, hydrabamines, imidazoles, lysines, methylamines, meglamines, *N*-methyl-*D*-glucamines, *N,N'*-dibenzylethylenediamines, nicotinamides, organic amines, ornithines, pyridines, picolies, piperazines, procain, tris(hydroxymethyl)methylamines, triethylamines, triethanolamines, trimethylamines, tromethamines and ureas.

[00156] In various embodiments, the salts may be formed by conventional means, such as by reacting the free base or free acid form of the product with one or more equivalents of the appropriate acid or base in a solvent or medium in which the salt is insoluble or in a solvent such as water, which is removed in vacuo or by freeze drying or by exchanging the ions of a existing salt for another ion or suitable ion-exchange resin.

Pharmaceutical composition

[00157] Another aspect of the present invention relates to a pharmaceutical composition including a pharmaceutically acceptable carrier and a compound according to the aspects of the present invention. The pharmaceutical composition can contain one or more of the above-identified compounds of the present invention. Typically, the pharmaceutical composition of the present invention will include a compound of the present invention or its pharmaceutically acceptable salt, as well as a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to any suitable adjuvants, carriers, excipients, or stabilizers, and can be in solid or liquid form such as, tablets, capsules, powders, solutions, suspensions, or emulsions.

[00158] Typically, the composition will contain from about 0.01 to 99 percent, preferably from about 20 to 75 percent of active compound(s), together with the adjuvants, carriers and/or excipients. While individual needs may vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typical dosages comprise about 0.01 to about 100 mg/kg body wt. The preferred dosages comprise about 0.1 to about 100 mg/kg body wt. The most preferred dosages comprise about 1 to about 100 mg/kg body wt. Treatment regimen for the administration of the compounds of the

present invention can also be determined readily by those with ordinary skill in art. That is, the frequency of administration and size of the dose can be established by routine optimization, preferably while minimizing any side effects.

[00159] The solid unit dosage forms can be of the conventional type. The solid form can be a capsule and the like, such as an ordinary gelatin type containing the compounds of the present invention and a carrier, for example, lubricants and inert fillers such as, lactose, sucrose, or cornstarch. In some embodiments, these compounds are tabulated with conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders like acacia, cornstarch, or gelatin, disintegrating agents, such as cornstarch, potato starch, or alginic acid, and a lubricant, like stearic acid or magnesium stearate.

[00160] The tablets, capsules, and the like can also contain a binder 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; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

[00161] Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets can be coated with shellac, sugar, or both. A syrup can contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor.

[00162] For oral therapeutic administration, these active compounds can be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compound in these compositions can, of course, be varied and can conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions according to the present invention are prepared so that an oral dosage unit contains between about 1 mg and 800 mg of active compound.

[00163] The active compounds of the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or they can be enclosed in hard or soft shell capsules, or they can be compressed into tablets, or they can be incorporated directly with the food of the diet.

[00164] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[00165] The compounds or pharmaceutical compositions of the present invention may also be administered in injectable dosages by solution or suspension of these materials in a physiologically acceptable diluent with a pharmaceutical adjuvant, carrier or excipient. Such adjuvants, carriers and/or

excipients include, but are not limited to, sterile liquids, such as water and oils, with or without the addition of a surfactant and other pharmaceutically and physiologically acceptable components. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions.

[00166] These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols such as, propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00167] For use as aerosols, the compounds of the present invention in solution or suspension may be packaged in a pressurized aerosol container together with suitable propellants, for example, hydrocarbon propellants like propane, butane, or isobutane with conventional adjuvants. The materials of the present invention also may be administered in a non-pressurized form such as in a nebulizer or atomizer.

[00168] In various embodiments, the compounds of this invention are administered in combination with an agent treating fibrosis. In some embodiment, the agent treating lung fibrosis is at least one selected from: pirfenidone and Nintedanib. Other examples of agents which can be useful in treating lung fibrosis including IPF, in combination with compound of the invention, include but are not limited to: Pioglitazone, Tralokinumab, Lebrikizumab, FG-3019, Simtuzumab, STX-100, BMS-986020, Rituximab, Carbon Monoxide, Azithromycin, and Cotrimoxazole. In various embodiments, the compounds of this invention are administered in combination with an agent treating NASH.

[00169] When administering the compounds of the present invention, they can be administered systemically or, alternatively, they can be administered directly to a specific site where fibrosis is present. Thus, administering can be accomplished in any manner effective for delivering the compounds or the pharmaceutical compositions to the fibrotic cells. Exemplary modes of administration include, without limitation, administering the compounds or compositions orally, topically, transdermally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes, such as, that of the nose, throat, and bronchial tubes.

Biological Activity

[00170] In various embodiments, the invention provides compounds and compositions, including any embodiment described herein, for use in any of the methods of this invention. In various embodiments, use of a compound of this invention or a composition comprising the same, will have utility in inhibiting, suppressing, enhancing or stimulating a desired response in a subject, as will be understood by one

skilled in the art. In some embodiments, the compositions may further comprise additional active ingredients, whose activity is useful for the particular application for which the compound of this invention is being administered.

[00171] The invention relates to the treatment, inhibition and reduction of fibrosis, including lung and hepatic fibrosis. More specifically, embodiments of the invention provide compositions and methods useful for the treatment and inhibition of fibrotic disorders, lung fibrosis, idiopathic pulmonary fibrosis (IPF), hepato-fibrotic conditions associated with Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH), employing the use of a compound according to this invention or a pharmaceutically acceptable salt thereof. In another embodiment, the human subject is afflicted with lung fibrosis. In another embodiment, the human subject is afflicted with idiopathic pulmonary fibrosis (IPF). In another embodiment, the human subject is afflicted with Non-Alcoholic Fatty Liver Disease (NAFLD). In another embodiment, the human subject is afflicted with Non-Alcoholic Steatohepatitis (NASH). In another embodiment, the human subject is not afflicted with Non-Alcoholic Steatohepatitis (NASH).

[00173] In various conditions, the formation of fibrotic tissue is characterized by the deposition of abnormally large amounts of collagen. The synthesis of collagen is also involved in a number of other pathological conditions. For example, clinical conditions and disorders associated with primary or secondary fibrosis, such as systemic sclerosis, graft-versus host disease (GVHD), pulmonary fibrosis and autoimmune disorders, are distinguished by excessive production of connective tissue, which results in the destruction of normal tissue architecture and function. These diseases can best be interpreted in terms of perturbations in cellular functions, a major manifestation of which is excessive collagen synthesis and deposition. The role of collagen in fibrosis has prompted attempts to develop drugs that inhibit its accumulation.

[00174] Excessive accumulation of collagen is the major pathologic feature in a variety of clinical conditions characterized by tissue fibrosis. These conditions include localized processes, as for example, pulmonary fibrosis and liver cirrhosis, or more generalized processes, like progressive systemic sclerosis. Collagen deposition is a feature of different forms of dermal fibrosis, which in addition to scleroderma, include localized and generalized morphea, keloids, hypertrophic scars, familial cutaneous collagenoma and connective tissue nevi of the collagen type. Recent advances in the understanding of the normal biochemistry of collagen have allowed us to define specific levels of collagen biosynthesis and degradation at which a pharmacologic intervention could lead to reduced collagen deposition in the tissues. Such compounds could potentially provide us with novel means to reduce the excessive collagen accumulation in diseases.

[00175] Accordingly, in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting fibrosis in a subject, comprising administering a compound according to this invention, to a subject suffering from fibrosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit fibrosis in said subject. In some embodiments, the fibrosis is systemic. In some embodiments, the fibrosis is organ specific. In some embodiments, the fibrosis is a result of wound healing. In some

embodiments, the fibrosis is a result of scarring. In some embodiments, the fibrosis is primary or secondary fibrosis. In some embodiments, the fibrosis is a result of systemic sclerosis, progressive systemic sclerosis, graft-versus host disease (GVHD), pulmonary fibrosis, autoimmune disorders, or any combination thereof; each represents a separate embodiment according to this invention. In another embodiment, the human subject is afflicted with lung fibrosis. In another embodiment, the human subject is afflicted with idiopathic pulmonary fibrosis (IPF). In some embodiments, the fibrosis is pulmonary fibrosis. In some embodiments, the subject has a liver cirrhosis. In some embodiments, the fibrosis is hepatic fibrosis, lung fibrosis or dermal fibrosis. In some embodiments, the dermal fibrosis is scleroderma. In some embodiments, the dermal fibrosis is a result of a localized or generalized morphea, keloids, hypertrophic scars, familial cutaneous collagenoma, connective tissue nevi of the collagen type, or any combination thereof; each represents a separate embodiment according to this invention. In some embodiments, the fibrosis results from tissue injury, inflammation, oxidative stress or any combination thereof; each represents a separate embodiment according to this invention. In some embodiments, the fibrosis is gingival fibromatosis. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compounds are selective to Collagen I. In some embodiments, the compounds are selective to Collagen IA. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compounds are selective to Collagen IA1. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00176] Human fibrotic diseases constitute a major health problem worldwide owing to the large number of affected individuals, the incomplete knowledge of the fibrotic process pathogenesis, the marked heterogeneity in their etiology and clinical manifestations, the absence of appropriate and fully validated biomarkers, and, most importantly, the current void of effective disease-modifying therapeutic agents. The fibrotic disorders encompass a wide spectrum of clinical entities including systemic fibrotic diseases such as systemic sclerosis (SSc), sclerodermatous graft vs. host disease, and nephrogenic systemic fibrosis, as well as numerous organ-specific disorders including radiation-induced fibrosis and cardiac, pulmonary, lung, liver, and kidney fibrosis. Although their causative mechanisms are quite diverse and, in several instances have remained elusive, these diseases share the common feature of an uncontrolled and progressive accumulation of fibrotic tissue in affected organs causing their dysfunction and ultimate failure. Despite the remarkable heterogeneity in the etiologic mechanisms responsible for the development of fibrotic diseases and in their clinical manifestations, numerous studies have identified activated myofibroblasts as the common cellular element ultimately responsible for the replacement of normal tissues with nonfunctional fibrotic tissue.

[00177] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting systemic fibrotic disease in a subject, comprising administering a compound according to this invention, to a subject suffering from a systemic fibrotic disease under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the systemic fibrotic disease in said subject. In some embodiments, the systemic

fibrotic disease is systemic sclerosis. In some embodiments, the systemic fibrotic disease is multifocal fibrosclerosis (IgG4-associated fibrosis). In some embodiments, the systemic fibrotic disease is nephrogenic systemic fibrosis. In some embodiments, the systemic fibrotic disease is sclerodermatous graft vs. host disease.

[00178] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an organ-specific fibrotic disease in a subject, comprising administering a compound according to this invention, to a subject suffering from an organ-specific fibrotic disease under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the organ-specific fibrotic disease in said subject.

[00179] In some embodiments, the organ-specific fibrotic disease is lung fibrosis. In some embodiments, the organ-specific fibrotic disease is idiopathic pulmonary fibrosis (IPF).

[00180] In some embodiments, the organ-specific fibrotic disease is cardiac fibrosis. In some embodiments, the cardiac fibrosis is hypertension-associated cardiac fibrosis. In some embodiments, the cardiac fibrosis is post-myocardial infarction. In some embodiments, the cardiac fibrosis is chagas disease-induced myocardial fibrosis.

[00181] In some embodiments, the organ-specific fibrotic disease is kidney fibrosis. In some embodiments, the kidney fibrosis is diabetic and hypertensive nephropathy. In some embodiments, the kidney fibrosis is urinary tract obstruction-induced kidney fibrosis. In some embodiments, the kidney fibrosis is inflammatory/autoimmune-induced kidney fibrosis. In some embodiments, the kidney fibrosis is aristolochic acid nephropathy. In some embodiments, the kidney fibrosis is polycystic kidney disease.

[00182] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cardiac fibrosis in a subject, comprising administering a compound of this invention, to a subject suffering from cardiac fibrosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit cardiac fibrosis in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00183] In some embodiments, the organ-specific fibrotic disease is pulmonary fibrosis. In some embodiments, the pulmonary fibrosis is idiopathic pulmonary fibrosis. In some embodiments, the pulmonary fibrosis is silica-induced pneumoconiosis (silicosis). In some embodiments, the pulmonary fibrosis is asbestos-induced pulmonary fibrosis (asbestosis). In some embodiments, the pulmonary fibrosis is chemotherapeutic agent-induced pulmonary fibrosis.

[00184] In some embodiments, the organ-specific fibrotic disease is liver and portal vein fibrosis. In some embodiments, the liver and portal vein fibrosis is alcoholic and nonalcoholic liver fibrosis. In some embodiments, the liver and portal vein fibrosis is hepatitis C-induced liver fibrosis. In some embodiments, the liver and portal vein fibrosis is primary biliary cirrhosis. In some embodiments, the liver and portal vein fibrosis is parasite-induced liver fibrosis (schistosomiasis).

[00185] In some embodiments, the organ-specific fibrotic disease is radiation-induced fibrosis (various organs). In some embodiments, the organ-specific fibrotic disease is bladder fibrosis. In some embodiments, the organ-specific fibrotic disease is intestinal fibrosis. In some embodiments, the organ-specific fibrotic disease is peritoneal sclerosis.

[00186] In some embodiments, the organ-specific fibrotic disease is diffuse fasciitis. In some embodiments, the diffuse fasciitis is localized scleroderma, keloids. In some embodiments, the diffuse fasciitis is dupuytren's disease. In some embodiments, the diffuse fasciitis is peyronie's disease. In some embodiments, the diffuse fasciitis is myelofibrosis. In some embodiments, the diffuse fasciitis is oral submucous fibrosis.

[00187] In some embodiments, the organ-specific fibrotic disease is a result of wound healing. In some embodiments, the organ-specific fibrotic disease is a result of scarring.

[00188] Fibrosis of the liver, also referred to herein as hepatic fibrosis, may be caused by various types of chronic liver injury, especially if an inflammatory component is involved. Self-limited, acute liver injury (e.g., acute viral hepatitis A), even when fulminant, does not necessarily distort the scaffolding architecture and hence does not typically cause fibrosis, despite loss of hepatocytes. However, factors such as chronic alcoholism, malnutrition, hemochromatosis, and exposure to poisons, toxins or drugs, may lead to chronic liver injury and hepatic fibrosis due to exposure to hepatotoxic chemical substances. Hepatic scarring, caused by surgery or other forms of injury associated with mechanical biliary obstruction, may also result in liver fibrosis.

[00189] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting hepatic fibrosis in a subject, comprising administering a compound of this invention, to a subject suffering from hepatic fibrosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit hepatic fibrosis in said subject. In some embodiments, the hepatic fibrosis results from hepatic scarring. In some embodiments, the hepatic fibrosis results from chronic liver injury. In some embodiments, the chronic liver injury results from chronic alcoholism, malnutrition, hemochromatosis, exposure to poisons, toxins or drugs; each represents a separate embodiment according to this invention. In some embodiments, the subject has a liver cirrhosis. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00190] Fibrosis itself is not necessarily symptomatic, however it can lead to the development of portal hypertension, in which scarring distorts blood flow through the liver, or cirrhosis, in which scarring results in disruption of normal hepatic architecture and liver dysfunction. The extent of each of these pathologies determines the clinical manifestation of hepato-fibrotic disorders. For example, congenital hepatic fibrosis affects portal vein branches, largely sparing the parenchyma. The result is portal hypertension with sparing of hepatocellular function.

[00191] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an hepato-fibrotic disorder in a subject, comprising administering a compound of this invention, to a subject suffering from hepato-fibrotic disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the hepato-fibrotic disorder in said subject. In some embodiments, the hepato-fibrotic disorder is: portal hypertension, cirrhosis, congenital hepatic fibrosis or any combination thereof; each represents a separate embodiment according to this invention. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00192] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting portal hypertension in a subject, comprising administering a compound of this invention, to a subject suffering from portal hypertension under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit portal hypertension in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00193] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cirrhosis in a subject, comprising administering a compound of this invention, to a subject suffering from cirrhosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit cirrhosis in said subject. In some embodiments, the cirrhosis is a result of hepatitis. In some embodiments, the cirrhosis is a result of alcoholism. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00194] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject, comprising administering a compound of this invention, to a subject suffering from alcoholism under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit alcoholism in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00195] Non-alcoholic steatohepatitis (NASH) and alcoholic steatohepatitis (ASH) have a similar pathogenesis and histopathology but a different etiology and epidemiology. NASH and ASH are advanced stages of non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD). NAFLD is characterized by excessive fat accumulation in the liver (steatosis), without any other evident

causes of chronic liver diseases (viral, autoimmune, genetic, etc.), and with an alcohol consumption ≤ 20-30 g/day. On the contrary, AFLD is defined as the presence of steatosis and alcohol consumption >20-30 g/day.

[00196] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting Non-alcoholic steatohepatitis (NASH) in a subject, comprising administering a compound of this invention, to a subject suffering from Non-alcoholic steatohepatitis (NASH) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit Non-alcoholic steatohepatitis (NASH) in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00197] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic steatohepatitis (ASH) in a subject, comprising administering a compound of this invention, to a subject suffering from alcoholic steatohepatitis (ASH) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit alcoholic steatohepatitis (ASH) in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00198] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non-alcoholic fatty liver disease (NAFLD) in a subject, comprising administering a compound of this invention, to a subject suffering from non-alcoholic fatty liver disease (NAFLD) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit non-alcoholic fatty liver disease (NAFLD) in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00199] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic fatty liver disease (AFLD) in a subject, comprising administering a compound of this invention, to a subject suffering from alcoholic fatty liver disease (AFLD) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit alcoholic fatty liver disease (AFLD) in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00200] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting lung fibrosis in a subject, comprising administering a compound of this invention, to a subject suffering from lung fibrosis under conditions

effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit lung fibrosis in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00201] Idiopathic pulmonary fibrosis (IPF) is an aging-associated recalcitrant lung disease with historically limited therapeutic options. The recent approval of two drugs, pirfenidone and nintedanib, by the United States Food and Drug Administration (FDA) in 2014 has heralded a new era in its management. Both drugs demonstrated efficacy in Phase III clinical trials by retarding the rate of progression of IPF; neither drug appears to be able to completely arrest disease progression. Advances in the understanding of IPF pathobiology have led to an unprecedented expansion in the number of potential therapeutic targets. Drugs targeting several of these are under investigation in various stages of clinical development.

[00202] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting idiopathic pulmonary fibrosis (IPF) in a subject, comprising administering a compound of this invention, to a subject suffering from idiopathic pulmonary fibrosis (IPF) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit idiopathic pulmonary fibrosis (IPF) in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**. In some embodiments, the compound is administered in combination with an agent treating IPF. In some embodiments, the compound is administered in combination with pirfenidone, nintedanib, or combination thereof; each represents a separate embodiment according to this invention.

[00203] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting dermal fibrosis in a subject, comprising administering a compound of this invention, to a subject suffering from dermal fibrosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit dermal fibrosis in said subject. In some embodiments, the dermal fibrosis is scleroderma. In some embodiments, the dermal fibrosis is a result of a localized or generalized morphea, keloids, hypertrophic scars, familial cutaneous collagenoma, connective tissue nevi of the collagen type, or any combination thereof; each represents a separate embodiment according to this invention. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00204] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting scleroderma in a subject, comprising administering a compound of this invention, to a subject suffering from scleroderma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit scleroderma in

said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00205] In various embodiments, this invention is directed to a method of inhibiting Collagen I (Col I) over production in a subject, comprising administering a compound of this invention, to a subject suffering from Collagen I (Col I) over production under conditions effective to inhibit Collagen I (Col I) over production in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compounds are Collagen I, II, II, IV, or V translation inhibitors; each represents a separate embodiment according to this invention. In some embodiments, the compounds are selective to Collagen I, II, II, IV, or V; each represents a separate embodiment according to this invention. In some embodiments, the compounds are selective to Collagen I. In some embodiments, the compounds are selective to Collagen IA. In some embodiments, the compounds are selective to Collagen IA1. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00206] In some embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject, comprising administering a compound of this invention, to a subject suffering from an autoimmune disease or disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the autoimmune disease or disorder in said subject. In some embodiments, the compound is a Collagen I translation inhibitor. In some embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention. In some embodiments, the compound is Compound **100**.

[00207] As used herein, subject or patient refers to any mammalian patient, including without limitation, humans and other primates, dogs, cats, horses, cows, sheep, pigs, rats, mice, and other rodents. In various embodiments, the subject is male. In some embodiments, the subject is female. In some embodiments, while the methods as described herein may be useful for treating either males or females.

[00208] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention.

EXAMPLES

General

[00209] All compounds were profiled for cellular potency in inhibition of collagen 1 (COL1) protein translation using a phenotypic screening platform.

EXAMPLE 1

Synthetic Details for Compounds 100-118 (Schemes 1-20)

General Methods

[00210] All reagents were commercial grade and were used as received without further purification, unless otherwise specified. Reagent grade solvents were used in all cases, unless otherwise specified. Thin layer chromatography was carried out using pre-coated silica gel F-254 plates (thickness 0.25 mm). ^{1}H-NMR and ^{19}F-NMR spectra were recorded on a Bruker Bruker Avance 400MHz or Avance III 400MHz spectrometer. The chemical shifts are expressed in ppm using the residual solvent as internal standard. Splitting patterns are designated as *s* (singlet), *d* (doublet), *dd* (doublet of doublets), *t* (triplet), *dt* (doublet of triplets), *q* (quartet), *m* (multiplet) and *br s* (broad singlet).

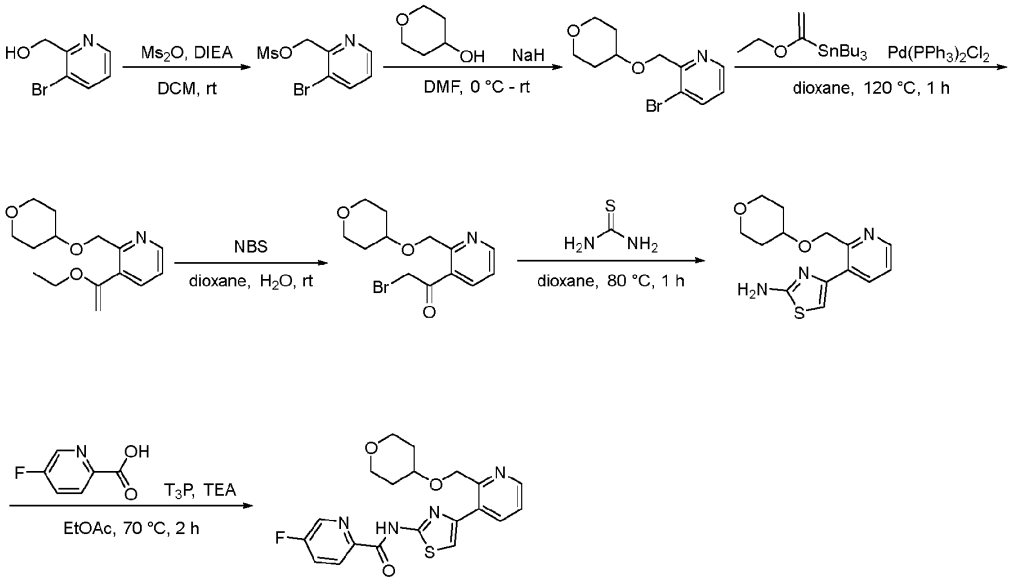
Abbreviations

AcOH	Acetic acid
amphos	*Bis*(di-*tert*-butyl(4-dimethylaminophenyl)phosphine
Boc	*tert*-Butyloxycarbonyl
BuLi	*n*-butyllithium
t-BuLi	*tert*-butyllithium
CDI	1,1′-Carbonyldiimidazole
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dppb	1,4-*Bis*(diphenylphosphino)butane
dppf	1,1′-*Bis*(diphenylphosphino)ferrocene
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMSO	Dimethylsulfoxide
EDC.HCl	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
HATU	[*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium-hexafluorophosphate]
HPLC	High performance liquid chromatography
MsCl	Methanesulfonyl chloride
NBS	*N*-Bromosuccinimide

NMP	*N*-Methyl-2-pyrrolidinone
rt	Room temperature
SEM	2-(Trimethylsilyl)ethoxymethyl
T3P	Propylphosphonic anhydride
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TCFH	*N*,*N*,*N*',*N*'-tetramethylchloroformamidinium hexafluorophosphate
THF	Tetrahydrofuran
TMS-OTf	Trimethylsilyl trifluoromethanesulfonate

Intermediates Preparation

Synthesis of 5-fluoro-*N*-(4-(2-(((tetrahydro-2*H*-pyran-4-yl)oxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide



Scheme 1. Synthesis of *5-fluoro-N-(4-(2-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide*

Synthesis of (3-bromopyridin-2-yl)methyl methanesulfonate

[00211] To a stirred solution of (3-bromopyridin-2-yl)methanol (100.00 g, 0.53 mol) and DIPEA (100.00 g, 0.77 mol) in DCM (1000 mL) was added Methanesulfonic anhydride (100.00 g, 0.57 mol) dropwise at 0 °C for over 10 min. The resulting mixture was stirred at room temperature for another 1 h under nitrogen atmosphere. After the reaction was completed, the resulting mixture was quenched by sat. $NaHCO_3$ aq. (1000 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 2000 mL). The combined organic layers were washed with brine (1 x 2000 mL), dried over anhydrous Na_2SO_4. After filtration, the

filtrate was concentrated under reduced pressure to afford 120.00 g crude product of (3-bromopyridin-2-yl)methyl methanesulfonate as purple solid.

[00212] Yield 120.00 g. m/z: [ESI$^+$] 266, 268 $(M + H)^+$.

Synthesis of 3-bromo-2-(((tetrahydro-*2H*-pyran-4-yl)oxy)methyl)pyridine

[00213] To a stirred solution of oxan-4-ol (69.00 g, 0.68 mol) in THF (1000 mL) was added NaH (30.00 g, 0.75 mmol, 60%) in portions at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 0 °C for another 0.5 h under nitrogen atmosphere. After that, 3-bromopyridin-2-yl)methyl methanesulfonate (120.00 g, crude) in THF (500 mL) was added dropwise for over 15 min at 0 °C. The resulting mixture was allowed to stir at room temperature for additional 1 h. After the reaction was completed, the reaction was quenched with 2000 mL sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 2000 mL). The combined organic layers were washed with brine (1 x 2000 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 85.00 g crude product of 3-bromo-2-[(oxan-4-yloxy)methyl]pyridine as brown oil.

[00214] Yield 85.00 g. m/z: [ESI$^+$] 272,274 $(M + H)^+$.

Synthesis of 3-(1-ethoxyvinyl)-2-(((tetrahydro-*2H*-pyran-4-yl)oxy)methyl)pyridine

[00215] To a stirred solution of 3-bromo-2-[(oxan-4-yloxy)methyl]pyridine (85.00 g, crude) and tributyl(1-ethoxyethenyl)stannane (140.00 g, 0.38 mol) in dioxane (1000 mL) was added $Pd(PPh_3)_2Cl_2$ (20.00 g, 0.03 mol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for another 2 h under nitrogen atmosphere. After the reaction was completed, the mixture was allowed to cool down to room temperature. The reaction mixture was concentrated under reduced pressure and the residue was used to the next step directly without further purification.

[00216] Used directly. m/z: [ESI$^+$] 264 $(M + H)^+$.

Synthesis of 2-bromo-1-(2-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)pyridin-3-yl)ethan-1-one

[00217] To a stirred solution of 3-(1-ethoxyethenyl)-2-[(oxan-4-yloxy)methyl]pyridine (crude product of previous step) in dioxane (1000 mL) and water (20 mL) was added NBS (55.00 g, 0.31 mol) in portions at 0 °C for over 5 min under nitrogen atmosphere. The resulting mixture was allowed to stir at room temperature for another 30 min under nitrogen atmosphere. After the reaction was completed, the reaction mixture was washed with brine (3 x 800 mL) and the organic layer was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford crude product of 2-bromo-1-(2-(((tetrahydro-*2H*-pyran-4-yl)oxy)methyl)pyridin-3-yl)ethan-1-one.

[00218] m/z: [ESI$^+$] 332 $(M + H + 18)^+$.

Synthesis of 4-(2-(((tetrahydro-*2H*-pyran-4-yl)oxy)methyl)pyridin-3-yl)thiazol-2-amine

[00219] To a stirred solution of 2-bromo-1-{2-[(oxan-4-yloxy)methyl]pyridin-3-yl}ethanone (crude product of previous step) in dioxane (600 mL) was added thiourea (20.00 g, 0.26 mol) in portions at room temperature under a nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 1 h under nitrogen

atmosphere. After the reaction was completed, the mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (1000 mL) and basified to pH 9 with saturated NaOH (aq.). The resulting mixture was extracted with EtOAc (5 x 2000 mL). The combined organic layers were washed with brine (1 x 2000 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 60 g crude product of 4-{2-[(oxan-4-yloxy)methyl]pyridin-3-yl}-1,3-thiazol-2-amine as yellow solid.

[00220] Yield 60.00 g (70% purity). m/z: [ESI$^+$] 292 $(M + H)^+$.

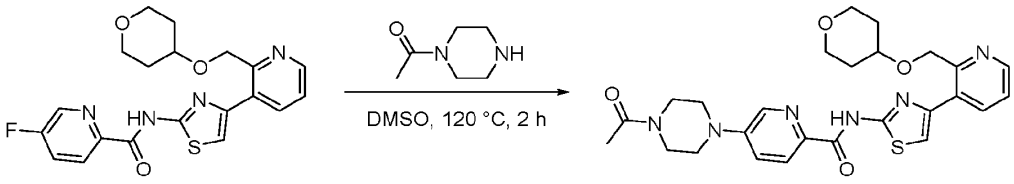
Synthesis of 5-fluoro-*N*-(4-(2-(((tetrahydro-2*H*-pyran-4-yl)oxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide

[00221] To a stirred solution of 4-{2-[(oxan-4-yloxy)methyl]pyridin-3-yl}-1,3-thiazol-2-amine (60.00 g, crude) and 5-fluoropyridine-2-carboxylic acid (30.00 g, 0.21 mol) in EtOAc (500 mL) was added T_3P (250.00 g, 0.39 mol 50%) dropwise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. After the reaction was completd, the mixture was allowed to cool down to room temperature. The resulting mixture was quenched with sat. $NaHCO_3$ (aq.) (1000 mL). The resulting mixture was extracted with EtOAc (5 x 2000 mL). The combined organic layers were washed with brine (1 x 2000 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-50% ethyl acetate in petroleum ether) and concentrated under reduced pressure to afford 28.00 g of 5-fluoro-N-(4-{2-[(oxan-4-yloxy)methyl]pyridin-3-yl}-1,3-thiazol-2-yl)pyridine-2-carboxamide as yellow solid.

[00222] Yield 28.00 g (13% over six steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 2.8 Hz, 1H), 8.55 (dd, J = 4.8, 1.6 Hz, 1H), 8.29 (dd, J = 8.8, 4.4 Hz, 1H), 8.12 – 7.99 (m, 2H), 7.65 (s, 1H), 7.47 (dd, J = 8.0, 4.8 Hz, 1H), 4.79 (s, 2H), 4.03 (q, J = 7.2 Hz, 1H), 3.73 (dt, J = 11.6, 4.2 Hz, 2H), 3.32 (s, 2H), 1.99 (s, 2H), 1.78 (dd, J = 13.0, 3.4 Hz, 2H). m/z: [ESI$^+$] 415 $(M + H)^+$.

Final Compounds

Synthesis of 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-(((tetrahydro-2*H*-pyran-4-yl)oxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide (Compound **100**)



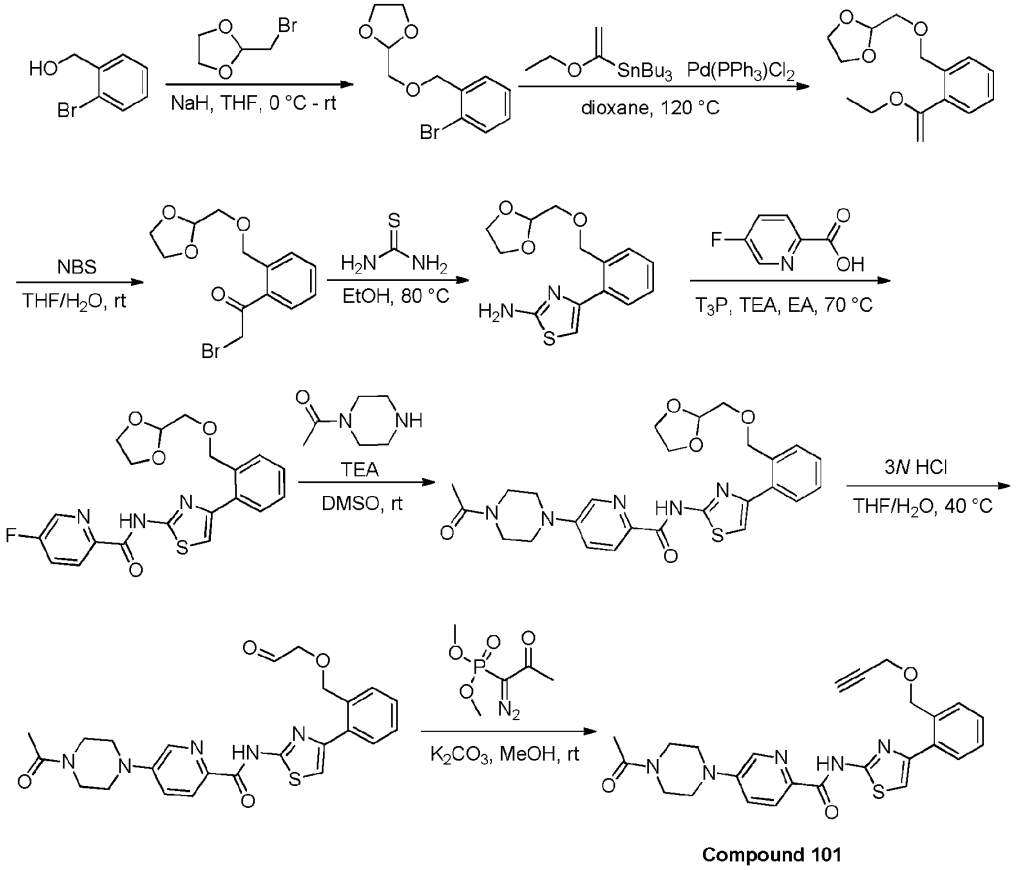
Compound 100

Scheme 2. Synthesis of *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide* (Compound **100**)

[00223] To a stirred solution of 5-fluoro-*N*-(4-{2-[(oxan-4-yloxy)methyl]pyridin-3-yl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (28.00 g, 0.08 mol) in DMSO (150 mL) was added 1-(piperazin-1-yl)ethanone

(28.00 g, 0.22 mol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 1 h under nitrogen atmosphere. After the reaction was completed, the mixture was allowed to cool down to room temperature. The residue was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 330 g; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 30% B - 50% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected and concentrated under reduced pressure. The residue was washed with EtOH (3 x 100 mL). The resulting solid was collected and dried under vacuum to afford 19.93 g of 5-(4-acetylpiperazin-1-yl)-N-(4-{2-[(oxan-4-yloxy)methyl]pyridin-3-yl}-1,3-thiazol-2-yl)pyridine-2-carboxamide as an off-white solid.

[00224] Yield 19.93 g (56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.55 (dd, J = 4.8, 1.6 Hz, 1H), 8.41 (d, J = 2.8 Hz, 1H), 8.09 (dd, J = 7.8, 1.6 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.60 (s, 1H), 7.48 (ddd, J = 14.0, 8.4, 3.6 Hz, 2H), 4.78 (s, 2H), 3.73 (dt, J = 11.8, 4.2 Hz, 2H), 3.66 – 3.55 (m, 5H), 3.47 (dt, J = 26.8, 5.6 Hz, 4H), 3.33 – 3.22 (m, 2H), 2.06 (s, 3H), 1.85 – 1.74 (m, 2H), 1.37 – 1.34 (m, 2H). m/z: [ESI$^+$] 523 (M + H)$^+$, ($C_{26}H_{30}N_6O_4S$).



Scheme 3. *Synthesis of 5-(4-formylpiperazin-1-yl)-N-(4-(2-((prop-2-yn-1-yloxy)methyl)phenyl)thiazol-2-yl)picolinamide (**Compound 101**)*

Synthesis of 2-(((2-bromobenzyl)oxy)methyl)-1,3-dioxolane

[00225] To a stirred solution of benzenemethanol, 2-bromo-(10.00 g, 53.466 mmol,) in DMF (25 mL, 323.039 mmol) was added NaH (4.28 g, 106.932 mmol, 60%) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere. Into above mixture was added 2-(bromomethyl)-1,3-dioxolane (13.39 g, 80.199 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 days under nitrogen atmosphere. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography: Column: silica-CS Column 330 g; Mobile Phase A:PE, Mobile Phase B: EA; Flow rate: 100 mL/min; Gradient: 0% B to 25% B in 40 min; 254/280 nm. The fractions containing the desired product were collected and concentrated under reduced pressure to afford 2-{[(2-bromophenyl)methoxy]methyl}-1,3-dioxolane as a yellow solid.

[00226] Yield 6.00 g (41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.51 (m, 2H), 7.37 - 7.31 (m, 1H), 7.20 -7.14 (m, 1H), 5.16 (t, J = 4.0 Hz, 1H), 4.70 (s, 2H), 4.07 - 4.02 (m, 2H), 3.96 - 3.92 (m, 2H), 3.67 (d, J = 4.0 Hz, 2H). m/z: [ESI$^+$] 273 $(M + H)^+$.

Synthesis of 2-(((2-(1-ethoxyvinyl)benzyl)oxy)methyl)-1,3-dioxolane

[00227] To a stirred solution of 2-{[(2-bromophenyl)methoxy]methyl}-1,3-dioxolane (5.00 g, 18.307 mmol) and tributyl(1-ethoxyethenyl)stannane (7.93 g, 21.968 mmol) in 1,4-dioxane (50 mL) was added $Pd(PPh_3)_2Cl_2$ (1.28 g, 1.831 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography: Column: silica-CS Column 330 g; Mobile Phase A: PE, Mobile Phase B: EA; Flow rate: 100 mL/min; Gradient: 0% B to 25% B in 40 min; 254/280 nm. The fractions containing the desired product were collected and concentrated under reduced pressure afford 2-({[2-(1-ethoxyethenyl)phenyl]methoxy}methyl)-1,3-dioxolane as a light yellow solid.

[00228] Yield 4.30 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 - 7.73 (m, 2H), 7.56 - 7.52 (m, 1H), 7.39 - 7.33 (m, 1H), 5.13 (t, J = 4.0 Hz, 1H), 4.73 (s, 2H), 4.34 - 4.32 (m, 1H), 4.27 - 4.25 (m, 1H), 4.03 (q, J = 7.2 Hz, 2H), 3.95 - 3.87 (m, 4H), 3.57 (d, J = 4.0 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H). m/z: [ESI$^+$] 265 $(M + H)^+$.

Synthesis of 1-(2-(((1,3-dioxolan-2-yl)methoxy)methyl)phenyl)-2-bromoethan-1-one

[00229] To a stirred solution of 2-({[2-(1-ethoxyethenyl)phenyl]methoxy}methyl)-1,3-dioxolane (4.30 g, 16.288 mmol) in THF (150 mL) and H_2O (9 mL) was added NBS (3.48 g, 19.545 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (150 mL), dried

over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-bromo-1-{2-[(1,3-dioxolan-2-ylmethoxy)methyl]phenyl}ethanone as a brown oil.

[00230] Yield 3.99 g (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 - 7.65 (m, 2H), 7.61 - 7.45 (m, 2H), 5.15 (t, J = 4.0 Hz, 1H), 4.87 (s, 2H), 4.50 (s, 2H), 4.08 - 3.97 (m, 2H), 3.96 - 3.88 (m, 2H), 3.65 (d, J = 4.0 Hz, 2H). m/z: [ESI$^+$] 315 $(M+H)^+$.

Synthesis of 4-(2-(((1,3-dioxolan-2-yl)methoxy)methyl)phenyl)thiazol-2-amine

[00231] To a stirred solution of 2-bromo-1-{2-[(1,3-dioxolan-2-ylmethoxy)methyl]phenyl}ethanone (3.99 g, 12.420 mmol) in EtOH (600 mL) was added thiourea (944 mg, 12.220 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 30 min under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography: Column: silica-CS Column 330 g; Mobile Phase A: PE, Mobile Phase B: EA; Flow rate: 100 mL/min; Gradient: 0% B to 25% B in 40 min; 254/280 nm. The fractions containing the desired product were collected and concentrated under reduced pressure to afford 4-{2-[(1,3-dioxolan-2-ylmethoxy)methyl]phenyl}-1,3-thiazol-2-amine as a light yellow solid.

[00232] Yield 1.20 g (32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 - 7.58 (m, 1H), 7.50 - 7.45 (m, 1H), 7.35 - 7.30 (m, 2H), 6.99 (s, 2H), 6.74 (s, 1H), 5.00 (t, J = 4.0 Hz, 1H), 4.66 (s, 2H), 3.93 - 3.87 (m, 2H), 3.86 - 3.77 (m, 2H), 3.49 (d, J = 4.0 Hz, 2H). m/z: [ESI$^+$] 293 $(M + H)^+$.

Synthesis of N-(4-(2-(((1,3-dioxolan-2-yl)methoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide

[00233] To a stirred solution of 4-{2-[(1,3-dioxolan-2-ylmethoxy)methyl]phenyl}-1,3-thiazol-2-amine (1.00 g, 3.421 mmol) and 5-fluoropyridine-2-carboxylic acid (579 mg, 4.103 mmol) in EA (10 mL) was added T_3P (3265 mg, 10.261 mmol) and TEA (1038 mg, 10.258 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: Column: C18 Column 120 g; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeCN; Flow rate: 80 mL/min; Gradient: 30% B to 50% B in 20 min; detector, UV 254/220 nm. The fractions containing the desired product were collected and concentrated under reduced pressure to afford *N*-(4-{2-[(1,3-dioxolan-2-ylmethoxy)methyl]phenyl}-1,3-thiazol-2-yl)-5-fluoropyridine-2-carboxamide as a brown solid.

[00234] Yield 1.02g (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 - 8.51 (m, 1H), 8.40 - 8.36 (m, 1H), 7.73 - 7.63 (m, 2H), 7.58 - 7.54 (m, 1H), 7.44 - 7.38 (m, 2H), 7.37 (s, 1H), 5.12 (t, J = 4.0 Hz, 1H), 4.74 (s, 2H), 4.04 - 4.00 (m, 2H), 3.95 - 3.91 (m, 2H), 3.62 (d, J = 4.0 Hz, 2H).m/z: [ESI$^+$] 416 $(M+H)^+$.

Synthesis of N-(4-(2-(((1,3-dioxolan-2-yl)methoxy)methyl)phenyl)thiazol-2-yl)-5-(4-acetylpiperazin-1-yl)picolinamide

[00235] To a stirred solution of *N*-(4-{2-[(1,3-dioxolan-2-ylmethoxy)methyl]phenyl}-1,3-thiazol-2-yl)-5-fluoropyridine-2-carboxamide (2.00 g, 4.814 mmol) and 1-(piperazin-1-yl)ethanone (1.23 g, 9.628 mmol) in DMSO (20 mL) was added TEA (974 mg, 9.625 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 100 ℃ for 3 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The residue was purified by reverse flash chromatography with the following conditions: Column: C18 Column 330 g; Mobile Phase A: water(10 mmol/L NH_4HCO_3), Mobile Phase B: MeCN; Flow rate: 100 mL/min; Gradient: 30% B to 50% B in 20 min; 254/220 nm. The fraction contained the desired product was collected and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-{2-[(1,3-dioxolan-2-ylmethoxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide as a brown solid.

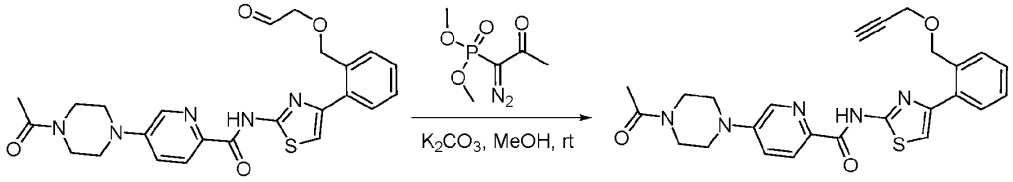
[00236] Yield 400 mg (54%). H-NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 7.73 - 7.68 (m, 1H), 7.58 - 7.53 (m, 1H), 7.40 - 7.36 (m, 2H), 7.29 (s, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 5.11 (t, *J* = 4.0 Hz, 1H), 4.74 (s, 2H), 4.01 - 3.98 (m, 2H), 3.93 - 3.90 (m, 2H), 3.86 - 3.82 (m, 2H), 3.72 - 3.67 (m, 2H), 3.60 (d, *J* = 4.0 Hz, 2H), 3.46 - 3.42 (m, 4H), 2.17 (s, 3H). m/z: [ESI^+] 390 $(M + H)^+$.

Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2,2-dihydroxyethoxy)methyl)phenyl)thiazol-2-yl)picolinamide

[00237] To a stirred solution of 5-(4-acetylpiperazin-1-yl)-*N*-(4-{2-[(1,3-dioxolan-2-ylmethoxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (400 mg, 0.764 mmol) in THF (4 mL, 3.056 mmol) was added HCl (4.00 mL, 12.002 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 40 ℃ for 3 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was basified to pH = 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography: Column: silica-CS Column 80 g; Mobile Phase A:PE, Mobile Phase B: EA; Flow rate: 40 mL/min; Gradient: 35% B to 55% B in 20 min; 254/280 nm to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-{2-[(2,2-dihydroxyethoxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide as an off-white solid. .

[00238] Yield 210 mg (55%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.43 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.76 - 7.66 (m, 1H), 7.61 - 7.48 (m, 2H), 7.45 - 7.33 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 4.66 (s, 2H), 3.69 - 3.57 (m, 4H), 3.56 - 3.48 (m, 2H), 3.48 - 3.42 (m, 2H), 3.26 (s, 2H), 2.07 (s, 3H). m/z: [ESI^+] 498 $(M + H)^+$.

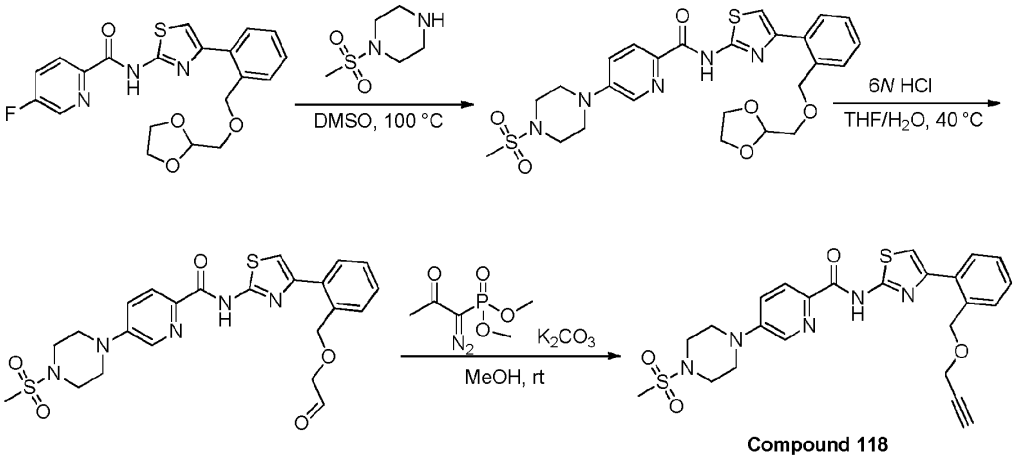
Synthesis of 5-(4-formylpiperazin-1-yl)-N-(4-(2-((prop-2-yn-1-yloxy)methyl)phenyl)thiazol-2-yl)picolinamide ***(Compound 101)***



[00239] To a stirred solution of 5-(4-acetylpiperazin-1-yl)-*N*-(4-{2-[(2-oxoethoxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (200 mg, 0.417 mmol) and seyferth-gilbert homologation (240 mg, 1.249 mmol) in MeOH (5 mL) was added K_2CO_3 (173 mg, 1.252 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 4 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5 µm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 52% B in 8 min; Wave Length: 254 nm;) to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-{2-[(prop-2-yn-1-yloxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide as an off-white solid..

[00240] Yield 30 mg (15%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.73 - 7.66 (m, 1H), 7.55 - 7.48 (m, 2H), 7.45 - 7.37 (m, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.37 (s, 1H), 4.75 (s, 2H), 4.22 (d, *J* = 2.4 Hz, 2H), 3.63 -3.60 (m, 4H), 3.54 - 3.50 (m, 2H), 3.47 - 3.42 (m, 2H), 3.33 (t, *J* = 2.4 Hz, 1H), 2.07 (s, 3H). m/z: [ESI+] 476 $(M + H)^+$.

Experimental procedures (Compound 118)



Scheme 4. *Synthesis of 5-(4-(methylsulfonyl)piperazin-1-yl)-N-(4-(2-((prop-2-yn-1-yloxy)methyl) phenyl)thiazol-2-yl)picolinamide ((**Compound 118**)*

Synthesis of N-(4-(2-(((1,3-dioxolan-2-yl)methoxy)methyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide

[00241] To a stirred solution of *N*-(4-(2-(((1,3-dioxolan-2-yl)methoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide (750 mg, 1.805 mmol) in DMSO (5 mL) was added 1-(methylsulfonyl)piperazine (900 mg, 5.480 mmol) in portions at room temperature. The resulting mixture was stirred at 100 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into 30 mL water. The precipitated solids were collected by filtration and washed with water (3 x 10 mL). This resulted in *N*-(4-(2-(((1,3-dioxolan-2-yl)methoxy)methyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide as a yellow solid.

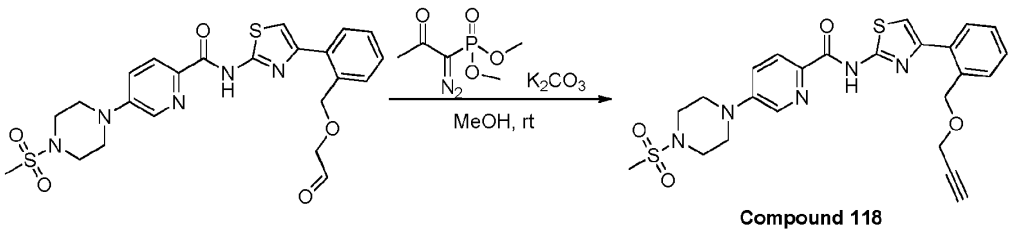
[00242] Yield 500 mg (49%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.32 (s, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.80 - 7.68 (m, 1H), 7.58 - 7.54 (m, 1H), 7.48 - 7.36 (m, 2H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.28 (s, 1H), 5.12 (t, *J* = 4.0 Hz, 1H), 4.74 (s, 2H), 4.08 - 3.84 (m, 4H), 3.62 (d, *J* = 4.0 Hz, 2H), 3.56 - 3.52 (m, 4H), 3.47 - 3.43 (m, 4H), 2.88 (s, 3H). m/z: [ESI$^+$] 560 $(M + H)^+$.

Synthesis of 5-(4-(methylsulfonyl)piperazin-1-yl)-N-(4-(2-((2-oxoethoxy)methyl)phenyl)thiazol-2-yl)picolinamide

[00243] To a stirred mixture of *N*-(4-(2-(((1,3-dioxolan-2-yl)methoxy)methyl)phenyl)thiazol-2-yl)-5-(4-(methylsulfonyl)piperazin-1-yl)picolinamide (500 mg, 0.893 mmol) in THF (10 mL) was added HCl (6 M) (10 mL) dropwise at room temperature. The resulting mixture was stirred at 40 °C for 16 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was basified to pH = 10 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 5-(4-(methylsulfonyl)piperazin-1-yl)-*N*-(4-(2-((2-oxoethoxy)methyl)phenyl)thiazol-2-yl)picolinamide as a yellow solid.

[00244] Yield 250 mg (54%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 9.75 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 7.77 - 7.65 (m, 1H), 7.63 - 7.53 (m, 1H), 7.47 - 7.39 (m, 2H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.22 (s, 1H), 4.84 (s, 2H), 4.16 (s, 2H), 3.56 - 3.52 (m, 4H), 3.48 - 3.44 (m, 4H), 2.86 (s, 3H). m/z: [ESI$^+$] 560 $(M + H)^+$.

Synthesis of 5-(4-(methylsulfonyl)piperazin-1-yl)-N-(4-(2-((prop-2-yn-1-yloxy)methyl)phenyl)thiazol-2-yl)picolinamide ***(Compound 118)***



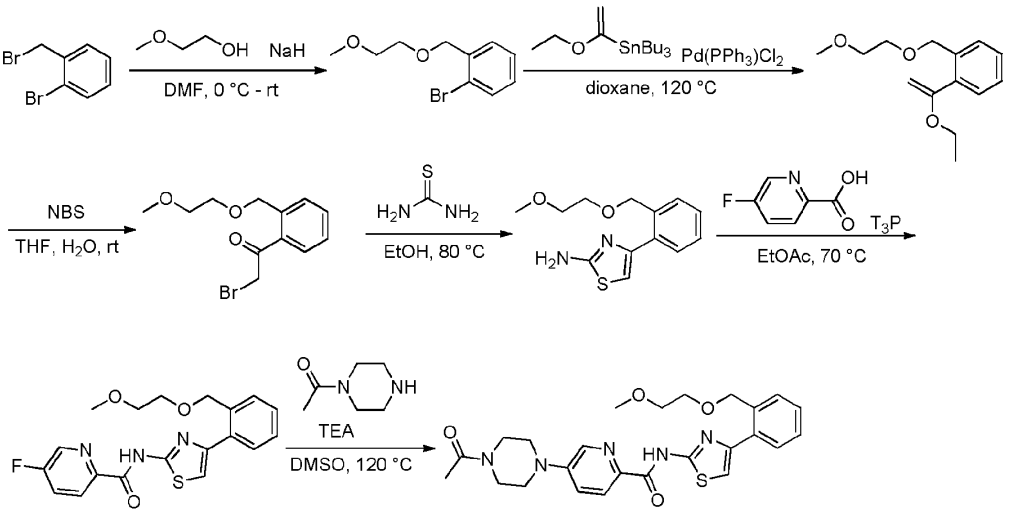
Compound 118

[00245] To a stirred solution of 5-(4-methanesulfonylpiperazin-1-yl)-*N*-(4-{2-[(2-oxoethoxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (250 mg, 0.485 mmol) and

seyferth-gilbert homologation (300 mg, 1.562 mmol) in MeOH (10 mL) was added K_2CO_3 (200 mg, 1.447 mmol) in portions at room temperature. The resulting mixture was stirred at 40°C for 16 h under nitrogen atmosphere. The resulting mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: Xselect CSH C18 OBD Column 30 x 150 mm 5 μm; Mobile Phase A: water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 52% B to 62% B in 10 min; Wave Length: 254 nm. The fractions containing the desired product were collected and concentrated under reduced pressure to afford 5-(4-methanesulfonylpiperazin-1-yl)-*N*-(4-{2-[(prop-2-yn-1-yloxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide as a white solid.

[00246] Yield 40 mg (16%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 8.47 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.76 - 7.64 (m, 1H), 7.58 - 7.49 (m, 2H), 7.45 - 7.32 (m, 2H), 7.30 (d, J = 8.8 Hz, 1H), 4.75 (s, 2H), 4.22 (d, J = 2.4 Hz, 2H), 3.61 - 3.57 (m, 4H), 3.45 (t, J = 2.4 Hz, 1H), 3.30 - 3.26 (m, 4H), 2.95 (s, 3H). m/z: [ESI$^+$] 512 (M + H)$^+$.

Experimental procedures (Compound 102)



Compound 102

Scheme 5. Synthesis of *5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-methoxyethoxy)methyl)phenyl)thiazol-2-yl)picolinamide* (**Compound 102**)

Synthesis of 1-bromo-2-((2-methoxyethoxy)methyl)benzene

[00247] To a stirred solution of 2-methoxyethanol (1.00 g, 13.141 mmol) in DMF (10 mL) was added NaH (1.05 g, 60%) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 30 min under nitrogen atmosphere. To the above mixture was added 1-bromo-2-(bromomethyl)benzene (4.93 g, 19.725 mmol) dropwise over 5 min at 0 °C. The resulting mixture was stirred at room temperature for additional 16 h. The reaction was quenched with sat. NH_4Cl (aq.) at room temperature. The resulting

mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography: Column: silica-CS Column 80 g; Mobile Phase A: PE, Mobile Phase B: EA; Flow rate: 60 mL/min; Gradient: 0% B to 25% B in 20 min; 254/280 nm to afford 1-bromo-2-[(2-methoxyethoxy)methyl]benzene as a white oil.

[00248] Yield 1.20 g (37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.49 (m, 2H), 7.33 - 7.30 (m, 1H), 7.17 - 7.10 (m, 1H), 4.64 (s, 2H), 3.71 (t, J = 6.0 Hz, 2H), 3.62 (t, J = 6.0 Hz, 2H), 3.42 (s, 3H). m/z: [ESI+] 245 $(M + H)^+$.

Synthesis of 1-(1-ethoxyvinyl)-2-((2-methoxyethoxy)methyl)benzene

[00249] To a stirred solution of 1-bromo-2-[(2-methoxyethoxy)methyl]benzene (1.20 g, 4.896 mmol) and tributyl(1-ethoxyethenyl)stannane (2.12 g, 5.875 mmol) in 1,4-dioxane (15 mL) was added $Pd(PPh_3)_2Cl_2$ (340 mg, 0.490 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was basified to pH = 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00250] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 - 7.45 (m, 2H), 7.39 - 7.32 (m, 2H), 4.69 (s, 2H), 4.32 (d, J = 2.0 Hz, 1H), 4.26 (d, J = 2.0 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 3.63 (t, J = 6.0 Hz, 2H), 3.60 (t, J = 6.0 Hz, 2H), 3.42 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H). m/z: [ESI+] 237 $(M + H)^+$.

Synthesis of 2-bromo-1-(2-((2-methoxyethoxy)methyl)phenyl)ethan-1-one

[00251] To a stirred solution of 1-(1-ethoxyethenyl)-2-[(2-methoxyethoxy)methyl]benzene (950 mg, 4.020 mmol) in THF (10 mL) and H_2O (0.5 mL) was added NBS (644 mg, 3.618 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00252] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.64 (m, 2H), 7.59 - 7.51 (m, 2H), 4.82 (s, 2H), 4.50 (s, 2H), 3.69 (t, J = 6.0 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.42 (s, 3H). m/z: [ESI+] 287 $(M + H)^+$.

Synthesis of 4-(2-((2-methoxyethoxy)methyl)phenyl)thiazol-2-amine

[00253] To a stirred solution of 2-bromo-1-{2-[(2-methoxyethoxy)methyl]phenyl}ethanone (800 mg, 2.786 mmol) in EtOH (10 mL) was added thiourea (254 mg, 3.337 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography: Column: silica-CS Column 80 g; Mobile Phase A: PE, Mobile Phase B: EA; Flow rate: 60 mL/min; Gradient: 30% B to 45%

B in 20 min; 254/280 nm to afford 4-{2-[(2-methoxyethoxy)methyl]phenyl}-1,3-thiazol-2-amine as a yellow oil.

[00254] Yield 526 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.62 (m, 1H), 7.53 - 7.49 (m, 1H), 7.37 - 7.32 (m, 2H), 6.80 (s, 1H), 5.40 (s, 2H), 4.66 (s, 2H), 3.66 (d, J = 6.0 Hz, 2H), 3.58 (d, J = 6.0 Hz, 2H), 3.40 (s, 3H). m/z: [ESI+] 265 $(M + H)^+$.

Synthesis of 5-fluoro-N-(4-(2-((2-methoxyethoxy)methyl)phenyl)thiazol-2-yl)picolinamide

[00255] To a stirred solution of 4-{2-[(2-methoxyethoxy)methyl]phenyl}-1,3-thiazol-2-amine (200 mg, 0.757 mmol) and 5-fluoropyridine-2-carboxylic acid (128 mg, 0.907 mmol) in EA (5 mL) were added T_3P (722 mg, 2.269 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 70 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

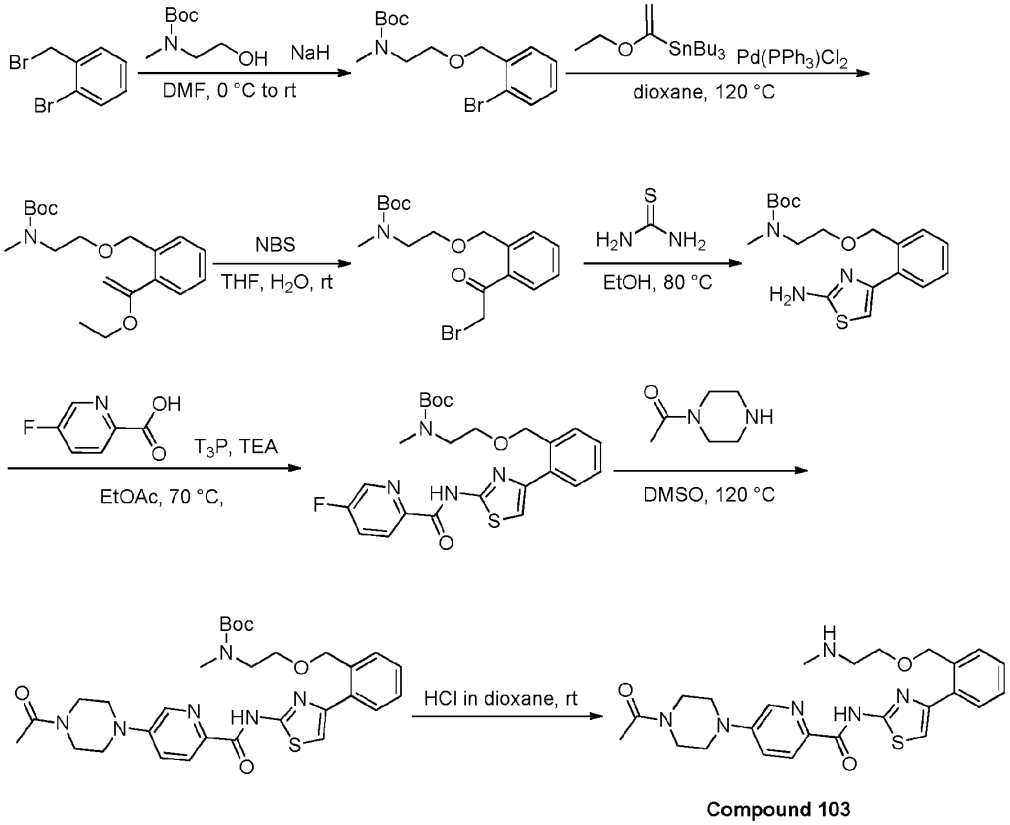
[00256] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 - 8.50 (m, 1H), 8.37 - 8.33 (m, 1H), 7.72 - 7.68 (m, 1H), 7.67 - 7.60 (m, 1H), 7.55 - 7.52 (m, 1H), 7.37 - 7.35 (m, 3H), 4.67 (s, 2H), 3.66 (t, J = 6.0 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 3.38 (s, 3H). m/z: [ESI+] 388 $(M + H)^+$.

Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-methoxyethoxy)methyl)phenyl)thiazol-2-yl)picolinamide ***(Compound 102)***

[00257] To a stirred solution of 5-fluoro-*N*-(4-{2-[(2-methoxyethoxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (150 mg, 0.387 mmol) and 1-(piperazin-1-yl)ethanone (100 mg, 0.780 mmol) in DMSO (3 mL) was added TEA (118 mg, 1.166 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 50% B in 10 min; Wave Length: 254 nm;) to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-{2-[(2-methoxyethoxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide) as a white solid.

[00258] Yield 15 mg mg (8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.74 - 7.67 (m, 1H), 7.58 - 7.48 (m, 2H), 7.46 (s, 1H), 7.44 - 7.35 (m, 2H), 4.67 (s, 2H), 3.66 - 3.57 (m, 5H), 3.54 - 3.47 (m, 3H), 3.47 - 3.43 (m, 2H), 3.35 - 3.30 (m, 5H), 2.07 (s, 3H). m/z: [ESI+] 496 $(M + H)^+$.

Experimental procedures (Compound 103)



Scheme 6. *Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylamino)ethoxy)methyl)phenyl) thiazol-2-yl)picolinamide ((**Compound 103**)*

Synthesis of tert-butyl (2-((2-bromobenzyl)oxy)ethyl)(methyl)carbamate

[00259] To a stirred mixture of *tert*-butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate (1.40 g, 8.002 mmol,) in DMF (20 mL) was added NaH (0.19 g, 8.002 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 30 min under nitrogen atmosphere. To the above mixture was added 1-bromo-2-(bromomethyl)benzene (2.00 g, 8.002 mmol) in portions over 5 min at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (3 x 500 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography: Column: silica-CS Column 80 g; Mobile Phase A: DCM, Mobile Phase B: MeOH; Flow rate: 60 mL/min; Gradient: 0% B to 10% B in 20 min; 254/280 nm to afford *tert*-butyl *N*-{2-[(2-bromophenyl)methoxy]ethyl}-*N*-methylcarbamate as a light yellow oil.

[00260] Yield (1.50 g 55%) ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.59 - 8.57 (m, 1H), 8.38 - 8.36 (m, 1H), 7.79 - 7.56 (m, 2H), 5.32 (s, 2H), 4.73 (t, *J* = 6.0 Hz, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.20 (s, 3H), 1.42 (s, 9H).

Synthesis of tert-butyl (2-((2-(1-ethoxyvinyl)benzyl)oxy)ethyl)(methyl)carbamate

[00261] To a stirred mixture of *tert*-butyl *N*-{2-[(2-bromophenyl) methoxy]ethyl}-*N*-methylcarbamate (1.50 g, 4.357 mmol) and tributyl(1-ethoxyethenyl)stannane (1.89 g, 5.228 mmol) in dioxane (20 mL) was added $Pd(PPh_3)_2Cl_2$ (0.31 g, 0.436 mmol)in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 90 °C for 1 h under nitrogen atmosphere. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in *tert*-butyl *N*-(2-{[2-(1-ethoxyethenyl)phenyl]methoxy}ethyl)-*N*-methylcarbamate as a black oil.

[00262] Yield (800 mg, 55%) ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.59 - 8.57 (m, 1H), 8.38 - 8.35 (m, 1H), 7.79 - 7.56 (m, 2H), 5.32 (d, *J* = 2.0 Hz, 1H), 5.30 (d, *J* = 2.0 Hz, 1H), 4.73 (s, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.22 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H)..

Synthesis of tert-butyl (2-((2-(2-bromoacetyl)benzyl)oxy)ethyl)(methyl)carbamate

[00263] To a stirred mixture of *tert*-butyl *N*-(2-{[2-(1-ethoxyethenyl)phenyl]methoxy}ethyl)-*N*-methylcarbamate (800 mg, 2.385 mmol) in THF (10 mL) and H_2O (1 mL) was added NBS (637 mg, 3.579 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (200 mL). The combined organic phase was washed with brine (2 x 100 mL), dried with Na_2SO_4. The filtrate was concentrated under reduced pressure. The crude (800 mg) was used for the next step directly without further purification.

Synthesis of tert-butyl (2-((2-(2-aminothiazol-4-yl)benzyl)oxy)ethyl)(methyl)carbamate

[00264] To a stirred solution of tert-butyl (2-((2-(2-bromoacetyl)benzyl)oxy)ethyl)(methyl)carbamate (800 mg, 2.076 mmol) in EtOH (10 mL) was added thiourea (158 mg, 4.156 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography: Column: silica-CS Column 80 g; Mobile Phase A: PE, Mobile Phase B: EA; Flow rate: 60 mL/min; Gradient: 30% B to 45% B in 20 min; 254/280 nm to afford *tert*-butyl (2-((2-(2-aminothiazol-4-yl)benzyl)oxy)ethyl)(methyl)carbamate as a yellow oil.

[00265] Yield (400 mg, 53%) ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.58-8.56 (m, 1H), 8.41-8.37 (m, 1H), 7.80-7.66 (m, 2H), 7.48 (s, 1H), 7.02 (s, 2H), 4.68 (s, 2H), 4.15 (t, *J* = 7.2 Hz, 2H), 3.65 (t, *J* = 7.2 Hz, 2H), 2.92 (s, 3H), 1.46 (s, 9H).

Synthesis of tert-butyl (2-((2-(2-(5-fluoropicolinamido)thiazol-4-yl)benzyl)oxy)ethyl)(methyl)carbamate

[00266] To a stirred mixture of *tert*-butyl *N*-(2-{[2-(2-amino-1,3-thiazol-4-yl)phenyl]methoxy}ethyl)-*N*-methylcarbamate (200 mg, 0.550 mmol), 5-fluoropyridine-2-carboxylic acid (93 mg, 0.659 mmol) and T_3P (525 mg, 1.650 mmol) in EA (5 mL) was added TEA (167 mg, 1.650 mmol) dropwise at room

temperature under nitrogen atmosphere. The resulting mixture was stirred at 70 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (100 mL). The combined organic phase was washed with brine (3 x 50 mL), dried with Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% to 70% ethyl acetate in petroleum ether to afford *tert*-butyl *N*-[2-({2-[2-(5-fluoropyridine-2-amido)-1,3-thiazol-4-yl]phenyl}methoxy)ethyl]-*N*-methylcarbamate as a light yellow oil.

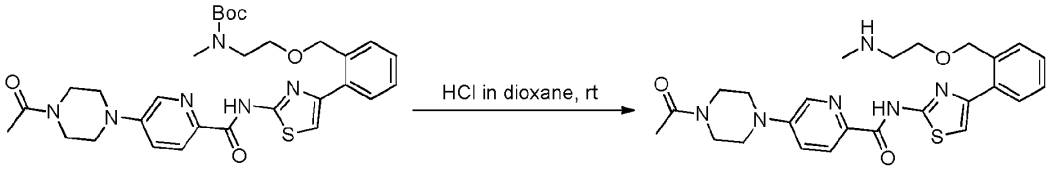
[00267] Yield (200 mg, 75%) ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.20-8.16 (m, 1H), 7.77-7.73 (m, 2H), 7.58-7.53 (m, 3H), 7.46-7.42 (m, 2H), 4.66 (s, 2H), 3.71 (t, *J* = 7.2 Hz, 2H), 3.46 (t, *J* = 7.2 Hz, 2H), 2.92 (s, 3H), 1.46 (s, 9H).

Synthesis of tert-butyl (2-((2-(2-(5-(4-acetylpiperazin-1-yl) picolinamido)thiazol-4-yl)benzyl)oxy)ethyl)(methyl)carbamate

[00268] To a stirred mixture of *tert*-butyl *N*-[2-({2-[2-(5-fluoropyridine-2-amido)-1,3-thiazol-4-yl]phenyl}methoxy)ethyl]-*N*-methylcarbamate (200 mg, 0.411 mmol) in DMSO (3 mL) was added 1-(piperazin-1-yl)ethanone (263 mg, 2.052 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 1 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20-40 μm, 120 g; Mobile Phase A: water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 60% B to 80% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected and concentrated under reduced pressure to afford *tert*-butyl *N*-{2-[(2-{2-[5-(4-acetylpiperazin-1-yl) pyridine-2-amido]-1,3-thiazol-4-yl}phenyl) methoxy]ethyl}-*N*-methylcarbamate as a light yellow solid.

[00269] Yield (150 mg, 61%) ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.20-8.16 (m, 1H), 7.77-7.73 (m, 2H), 7.54 (s, 1H), 7.47-7.44 (m, 2H), 4.66 (s, 2H), 3.71 (t, *J* = 7.2 Hz, 2H), 3.55-3.50 (m, 4H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.42-3.38 (m, 4H), 2.92 (s, 3H), 2.13 (s, 3H), 1.46 (s, 9H).

Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylamino)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide ***(Compound 103)***



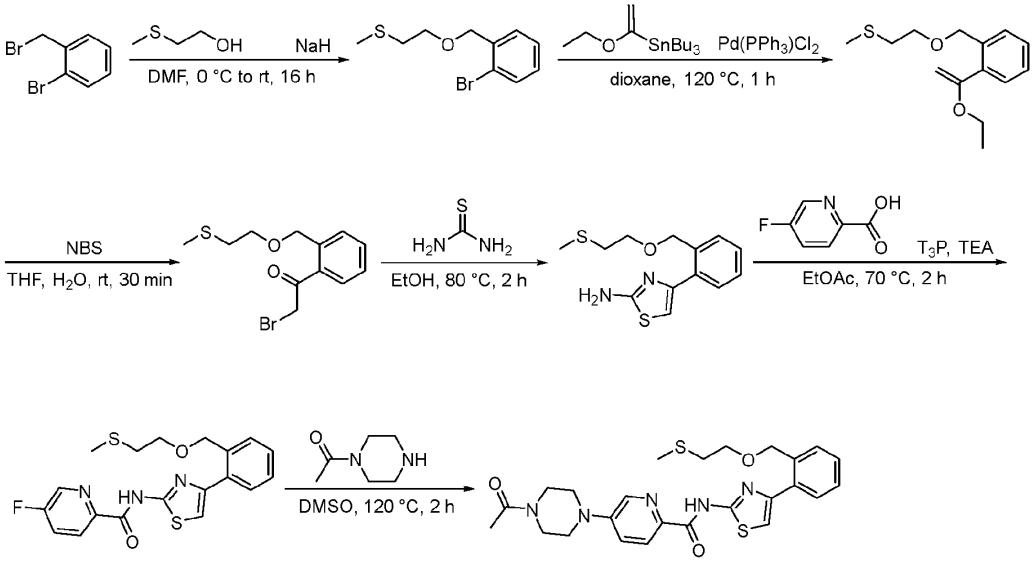
Compound 103

[00270] A mixture of tert-butyl *N*-{2-[(2-{2-[5-(4-acetylpiperazin-1-yl)pyridine-2-amido]-1,3-thiazol-4-yl}phenyl)methoxy]ethyl}-*N*-methylcarbamate (150 mg, 0.252 mmol) and HCl (gas) in 1,4-dioxane (2 mL, 8.000 mmol) in DCM (4 mL) was stirred at room temperature for 1 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (3 mL).

The mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20-40 μm, 120 g; Mobile Phase A: water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 40% B to 60% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylamino)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide as a brown yellow solid.

[00271] Yield 39 mg (31%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.05-8.02 (m, 1H), 7.74-7.65 (m, 1H), 7.53-7.52 (m, 2H), 7.49-7.29 (m, 3H), 4.62 (s, 2H), 3.71 (t, J = 7.2 Hz, 2H), 3.70-3.55 (m, 4H), 3.49-3.45 (m, 4H), 2.67 (t, J = 7.2 Hz, 2H), 2.30 (s, 3H), 2.07 (s, 3H).

***Experimental Procedure* (*Compound 104*)**



Compound 104

Scheme 7. *Synthesis of* 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylthio)ethoxy)methyl)phenyl) thiazol-2-yl)picolinamide (***Compound 104***)

Synthesis of (2-((2-bromobenzyl)oxy)ethyl)(methyl)sulfane

[00272] To a solution of 2-(methylthio)ethan-1-ol (5.53 g, 60.01 mmol) in DMF (50 mL) was added NaH (0.96 g, 40.01 mmol) at 0 °C. The mixture was stirred for 15 min. 1-bromo-2-(bromomethyl)benzene (5.00 g, 20.01 mmol) was added and the mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (10/1) and concentrated under reduced pressure to afford (2-((2-bromobenzyl)oxy)ethyl)(methyl)sulfane as a colorless oil.

[00273] Yield 2.00 g (38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.34 (td, J = 7.6, 1.2 Hz, 1H), 7.17 (td, J = 7.6, 1.2 Hz, 1H), 4.64 (s, 2H), 3.78 (t, J = 6.8 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H), 2.19 (s, 3H). m/z: [ESI$^+$] 261, 263 $(M + H)^+$.

Synthesis of (2-((2-(1-ethoxyvinyl)benzyl)oxy)ethyl)(methyl)sulfane

[00274] To a stirred mixture of (2-((2-bromobenzyl)oxy)ethyl)(methyl)sulfane (2.00 g, 7.65 mmol) and tributyl(1-ethoxyethenyl)stannane (4.15 g, 11.48 mmol) in dioxane (20 mL) was added $Pd(PPh_3)_2Cl_2$ (0.54 g, 0.76 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was basified to pH 9 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford (2-((2-(1-ethoxyvinyl)benzyl)oxy)ethyl)(methyl)sulfane as a yellow oil.

[00275] Yield 1.30 g (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.59 (m, 2H), 7.42-7.40 (m, 1H), 7.21-7.19 (m, 1H), 3.81 (s, 2H), 2.81-2.79 (m, 2H), 2.62 (q, J = 8.0, 2H), 2.18 (t, J = 6.8 Hz, 2H), 1.68 (t, J = 6.8 Hz, 2H), 1.33 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H). m/z: [ESI$^+$] 253 $(M + H)^+$.

Synthesis of 2-bromo-1-(2-((2-(methylthio)ethoxy)methyl)phenyl)ethan-1-one

[00276] A mixture of (2-((2-(1-ethoxyvinyl)benzyl)oxy)ethyl)(methyl)sulfane (300 mg, 1.18 mmol) and NBS (190 mg, 1.06 mmol) in THF (3 mL) and H_2O (0.15 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-bromo-1-(2-((2-(methylthio)ethoxy)methyl)phenyl)ethan-1-one as a yellow oil.

Yield 120 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 6.4 Hz, 1H), 7.61 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 6.4 Hz, 1H), 7.34 (t, J = 6.8 Hz, 1H), 4.67 (s, 2H), 3.67 (s, 2H), 2.58 (t, J = 8.0 Hz, 2H), 2.18 (t, J = 8.0 Hz, 2H), 1.69 (s, 3H). m/z: [ESI$^+$] 314, 303 $(M + H)^+$.

Synthesis of 4-(2-((2-(methylthio)ethoxy)methyl)phenyl)thiazol-2-amine

[00277] A mixture of 2-bromo-1-(2-((2-(methylthio)ethoxy)methyl)phenyl)ethan-1-one (120 mg, 0.396 mmol) and thiourea (36 mg, 0.473 mmol) in EtOH (2 mL) was stirred at 80 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1/2) and concentrated under reduced pressure to afford 4-(2-((2-(methylthio)ethoxy)methyl)phenyl)thiazol-2-amine as a yellow oil.

[00278] Yield 90 mg (81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47-7.66 (m, 4H), 7.06 (s, 1H), 7.04 (s, 2H), 4.70 (s, 2H), 3.72 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 2.16 (s, 3H). m/z: [ESI$^+$] 281 $(M+H)^+$.

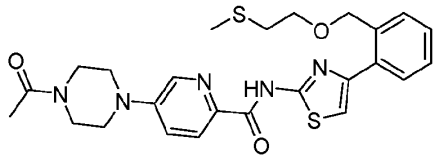
Synthesis of 5-fluoro-*N*-(4-(2-((2-(methylthio)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide

[00279] To a stirred solution of 4-(2-((2-(methylthio)ethoxy)methyl)phenyl)thiazol-2-amine (300 mg, 1.070 mmol) and 5-fluoropyridine-2-carboxylic acid (543 mg, 3.848 mmol) in EtOAc (3 mL) was added T_3P (1021 mg, 3.209 mmol) and TEA (0.5 mL) at room temperature . The resulting mixture was stirred at 70 °C for 2 h. The mixture was allowed to cool down to room temperature. Desired product could be detected by LCMS. The mixture was basified to pH 9 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1) and concentrated under reduced pressure to afford 5-fluoro-*N*-(4-(2-((2-(methylthio)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide as a light yellow solid.

[00280] Yield 90 mg (21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 8.55 (d, J = 2.8 Hz, 1H), 8.39 (dd, J = 8.4, 4.4 Hz, 1H), 7.77-7.70 (m, 1H), 7.60-7.38 (m, 4H), 7.34 (s, 1H), 4.70 (s, 2H), 3.72 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 2.16 (s, 3H). m/z: [ESI$^+$] 404 $(M+H)^+$.

Final Compounds

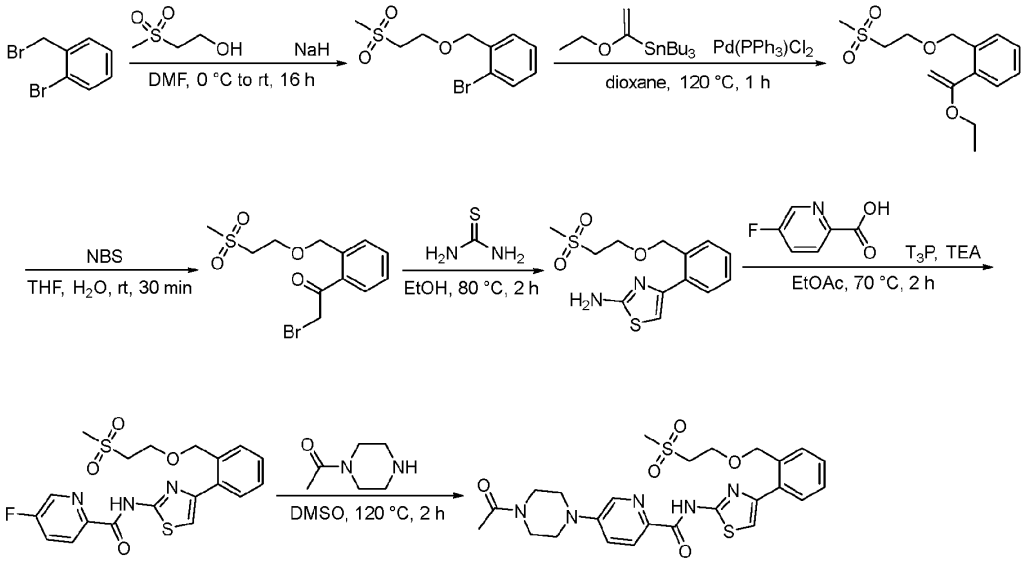
Synthesis of 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylthio)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide (***Compound 104***)



[00281] A solution of 5-fluoro-*N*-(4-(2-((2-(methylthio)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide (90 mg, 0.223 mmol) and 1-(piperazin-1-yl)ethan-1-one (86 mg, 0.671 mmol) in DMSO (1 mL) was stirred at 120 °C for 2 h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The crude product (90 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 47% B to 52% B in 8 min, 52% B; Wave Length: 254 nm; RT1(min): 7.5; Number Of Runs: 0) and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-[4-(2-{[2-(methylsulfanyl)ethoxy]methyl}phenyl)-1,3-thiazol-2-yl]pyridine-2-carboxamide as a yellow semi-solid.

[00282] Yield 60 mg (53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 8.42 (d, J = 2.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.73-7.64 (m, 1H), 7.57-7.55 (m, 1H), 7.52-7.50 (m, 1H), 7.46 (s, 1H), 7.43-7.34 (m, 2H), 4.69 (s, 2H), 3.66-3.62 (m, 6H), 3.51 (d, J = 5.8 Hz, 2H), 3.44 (t, J = 5.2 Hz, 2H), 2.67 (t, J = 6.0 Hz, 2H), 2.06 (s, 3H), 2.04 (s, 3H). m/z: [ESI$^+$] 512 $(M + H)^+$. ($C_{25}H_{29}N_5O_3S_2$).

***Experimental procedure* (*Compound 105*)**



Compound 105

Scheme 8. *Synthesis of* 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl) phenyl) thiazol-2-yl)picolinamide (***Compound 105***)

Synthesis of 1-bromo-2-((2-(methylsulfonyl)ethoxy)methyl)benzene

[00283] To a solution of 2-(methylsulfonyl)ethan-1-ol (1.49 g, 12.01 mmol) in DMF (20 mL) was added NaH (0.38 g, 16.04 mmol) at 0 °C. The mixture was stirred for 15 min. 1-bromo-2-(bromomethyl)benzene (2.00 g, 8.02 mmol) was added and the mixture was allowed to warm to rt and stirred for 1 h. The mixture was basified to pH 8 with saturated NH_4Cl (aq.). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1/1) to afford 1-bromo-2-((2-(methylsulfonyl)ethoxy)methyl)benzene as a white oil.

[00284] Yield 1.40 g (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.0, 1.2 Hz, 1H), 7.43 (dd, J = 7.6, 1.6 Hz, 1H), 7.35 (td, J = 7.6, 1.2 Hz, 1H), 7.21 (td, J = 7.6, 1.6 Hz, 1H), 4.66 (s, 2H), 4.06 (t, J = 6.0 Hz, 2H), 3.30 (t, J = 6.0 Hz, 2H), 3.03 (s, 3H). m/z: [ESI$^+$] 293, 295 $(M + H)^+$.

Synthesis of 1-(1-ethoxyvinyl)-2-((2-(methylsulfonyl)ethoxy)methyl)benzene

[00285] To a stirred mixture of 1-bromo-2-((2-(methylsulfonyl)ethoxy)methyl)benzene (1.40 g, 4.77 mmol) and tributyl(1-ethoxyvinyl)stannane (2.59 g, 7.16 mmol) in dioxane (20 mL) was added $Pd(PPh_3)_2Cl_2$ (0.34 g, 0.478 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was basified to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (1 x 100 mL). The combined organic layers were washed with brine (3 x

100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 1-(1-ethoxyvinyl)-2-((2-(methylsulfonyl)ethoxy)methyl)benzene as a black oil.

[00286] Yield 1.10 g (81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.30 (m, 4H), 4.69 (s, 2H), 4.25-4.23 (m, 2H), 3.99-3.93 (m, 4H), 3.01 (t, J = 4.4 Hz, 2H), 3.03 (s, 3H), 1.39 (t, J = 2.0 Hz, 3H). m/z: [ESI$^+$] 285 $(M + H)^+$.

Synthesis of 2-bromo-1-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)ethan-1-one

[00287] A mixture of 1-(1-ethoxyvinyl)-2-((2-(methylsulfonyl)ethoxy)methyl)benzene (1.10 g, 3.86 mmol) and NBS (0.76 g, 4.25 mmol) in THF (15 mL) and H_2O (3 mL) was stirred at room temperature for 30 min. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (1 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-bromo-1-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)ethan-1-one as a black oil.

[00288] Yield 900 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.32 (m, 4H), 4.66 (s, 2H), 4.14 (s, 2H), 3.46 (t, J = 7.2 Hz, 2H), 2.88 (t, J = 7.2 Hz, 2H), 2.80 (s, 3H). m/z: [ESI$^+$] 335, 337 $(M + H)^+$.

Synthesis of 4-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)thiazol-2-amine

[00289] A solution of 2-bromo-1-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)ethan-1-one (900 mg, 2.685 mmol) and thiourea (245 mg, 3.219 mmol) in EtOH (10 mL) was stirred at 80 °C for 2 h. The mixture was allowed to cool down to room temperature. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/2) and concentrated under reduced pressure to afford 4-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)thiazol-2-amine as a yellow solid.

[00290] Yield 700 mg (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.31 (m, 4H), 6.59 (s, 1H), 4.62 (s, 2H), 4.04-3.91 (m, 2H), 3.30-3.23 (m, 2H), 3.03 (s, 3H). m/z: [ESI$^+$] 313 $(M + H)^+$.

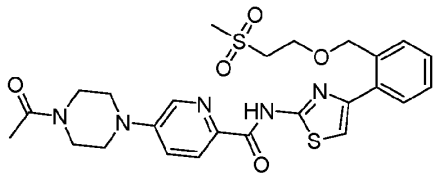
Synthesis of 5-fluoro-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide

[00291] To a stirred mixture of 4-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)thiazol-2-amine (700 mg, 2.241 mmol) and 5-fluoropyridine-2-carboxylic acid (379 mg, 2.686 mmol) in EtOAc (10 mL) was added T_3P (2139 mg, 6.723 mmol) and DIEA (1 mL) at room temperature. The resulting mixture was stirred at 70 °C for 2 h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1/1) and concentrated under reduced pressure to afford 5-fluoro-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide as a yellow solid.

[00292] Yield 300 mg (31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.60-8.53 (m, 1H), 8.39-8.34 (m, 1H), 7.73-7.60 (m, 2H), 7.58-7.47 (m, 1H), 7.47-7.36 (m, 2H), 7.16 (s, 1H), 4.75 (s, 2H), 3.99 (t, J = 5.2 Hz, 2H), 3.27 (t, J = 5.2 Hz, 2H), 3.03 (s, 3H). m/z: [ESI$^+$] 436 $(M + H)^+$.

Final Compounds

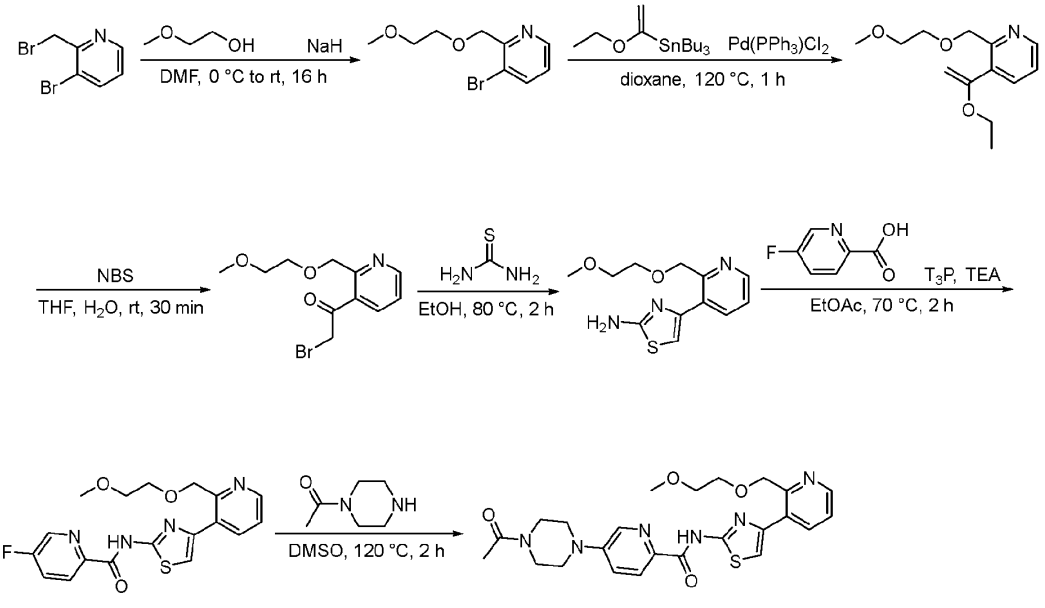
Synthesis of 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl) phenyl)thiazol-2-yl)picolinamide (***Compound 105***)



[00293] A solution of 5-fluoro-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl)phenyl)thiazol-2-yl)picolinamide (90 mg, 0.21 mmol) and 1-(piperazin-1-yl)ethanone (79 mg, 0.61 mmol) in DMSO (1 mL) was stirred at 120 °C for 2 h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with the following conditions: Column, Spherical C18, 20 - 40 um,120; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B; Flow rate: 80 mL/min; Gradient:40% to 60%B in 20 min; Detector, UV 254 nm. The fractions containing desired product were collected at 54% B and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylsulfonyl)ethoxy) methyl)phenyl)thiazol-2-yl)picolinamide as a white solid.

[00294] Yield 68 mg (61%). ^{1}H NMR (400 MHz, DMSO) δ 11.64 (s, 1H), 8.43 (d, *J* = 2.8 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.73-7.67 (m, 1H), 7.61-7.48 (m, 2H), 7.44 (s, 1H), 7.43- 7.32 (m, 2H), 4.75 (s, 2H), 3.86 (t, *J* = 5.6 Hz, 2H), 3.73-3.58 (m, 4H), 3.57- 3.49 (m, 2H), 3.49-3.39 (m, 4H), 2.95 (s, 3H), 2.07 (s, 3H). m/z: [ESI$^+$] 544 $(M + H)^+$, ($C_{25}H_{29}N_5O_5S_2$).

Experimental procedures (***Compound 108***)



Compound 108

Scheme 9. *Synthesis of* 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl) thiazol-2-yl)picolinamide (***Compound 108***)

Synthesis of 3-bromo-2-((2-methoxyethoxy)methyl)pyridine

[00295] To a stirred solution of 2-methoxyethan-1-ol (0.45 g, 5.98 mmol) in DMF (15 mL) was added sodium hydride (0.32 g, 7.97 mmol) in portions at 0 °C. The resulting mixture was stirred at 0°C for 30 min. To the above mixture was added 3-bromo-2-(bromomethyl)pyridine (1.00 g, 3.99 mmol) in DMF (5 mL) dropwise over 1 min at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. NH_4Cl (aq.) (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 30% to 50% ethyl acetate in petroleum ether and concentrated under reduced pressure to afford 3-bromo-2-[(2-methoxyethoxy)methyl]pyridine as a yellow oil.

[00296] Yield 0.27 g (27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.8, 1.6 Hz, 1H), 7.95 (dd, J = 8.0, 1.6 Hz, 1H), 7.20 (dd, J = 8.0, 4.8 Hz, 1H), 4.87 (s, 2H), 3.86-3.77 (m, 2H), 3.70-3.61 (m, 2H), 3.41 (s, 3H). m/z: [ESI$^+$] 246, 248 $(M + H)^+$.

Synthesis of 3-(1-ethoxyvinyl)-2-((2-methoxyethoxy)methyl)pyridine

[00297] To a stirred solution 2-bromo-3-[(2-methoxyethoxy)methyl]pyridine (0.27 g, 1.10 mmol) and tributyl(1-ethoxyvinyl)stannane (594 mg, 1.65 mmol) in1,4-dioxane (5 mL) was added dichloropalladium; bis(triphenylphosphane) (77 mg, 0.11 mmol) in portions at room temperature .The resulting mixture was stirred at 100 °C for 1 h. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with EtOAc (1 x 100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 3-(1-ethoxyvinyl)-2-((2-methoxyethoxy)methyl)pyridine as a brown oil. The crude product mixture was used in the next step directly without further purification.

[00298] Yield 0.25 g (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.44 (m, 3H), 4.79 (s, 2H), 4.42-4.40 (m, 2H), 3.93 (q, J = 7.0 Hz, 2H), 3.71 (dd, J = 6.0, 3.6 Hz, 2H), 3.65-3.61 (m, 4H), 3.39 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H).m/z: [ESI$^+$] 238$(M + H)^+$.

Synthesis of 2-bromo-1-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)ethan-1-one

[00299] A mixture of 3-(1-ethoxyvinyl)-2-((2-methoxyethoxy)methyl)pyridine (270 mg, 1.14 mmol) and *N*-bromosuccinimide (243 mg, 1.37 mmol) in THF (20 mL) and H_2O (1 mL) was stirred at room temperature for 1 h. The resulting mixture was extracted with EtOAc (1 x 100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-bromo-1-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)ethan-1-one as a brown oil.

[00300] Yield 0.30 g (92%). m/z: [ESI$^+$] 288, 290 $(M + H)^+$.

Synthesis of 4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)thiazol-2-amine

[00301] To a stirred mixture of 2-bromo-1-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)ethan-1-one (1 g, 3.47 mmol) in C_2H_5OH (10 mL) was added thiourea (0.53 g, 6.94 mmol) at room temperature .The resulting mixture was stirred at 80 °C for 1 h. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with EtOAc (1 x 100mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 330 g; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 30% B to 50% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected at 40% B and concentrated under reduced pressure to afford 4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)thiazol-2-amine as a yellow oil.

[00302] Yield 84 mg (9 %) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65-8.60 (m, 1H), 7.85-7.34 (m, 3H), 4.90 (s, 2H), 3.68 (dd, *J* = 5.6, 3.2 Hz, 2H), 3.57 (dd, *J* = 5.6, 3.2 Hz, 2H), 2.61 (s, 3H). m/z: [ESI$^+$] 266 $(M + H)^+$.

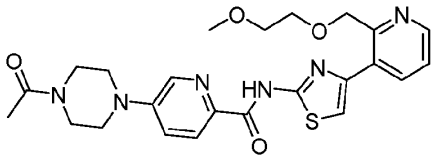
Synthesis of 5-fluoro-*N*-(4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide

[00303] To a stirred solution 4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)thiazol-2-amine (254 mg, 0.96 mmol) and 5-fluoropicolinic acid (270 mg, 1.91 mmol) in ethyl acetate (2 mL) were added triethylamine (291 mg, 2.88 mmol) and tripropyl-1,3,5,2lambda5,4lambda5,6lambda5-trioxatriphosphinane-2,4,6-trione (1827 mg, 2.87 mmol) at room temperature .The resulting mixture was stirred at 120 °C for 2 h. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with EtOAc (1 x 100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 330 g; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 30% B - 60% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected at 40% B and concentrated under reduced pressure to afford 5-fluoro-*N*-(4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide as a white solid.

[00304] Yield 50 mg (13%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56-8.32 (m, 2H), 7.96 (s, 1H), 7.69-7.61 (m, 4H), 4.44 (s, 2H), 3.70-3.62 (m, 4H), 3.41 (s, 3H). m/z: [ESI$^+$] 389 $(M + H)^+$.

Final Compounds

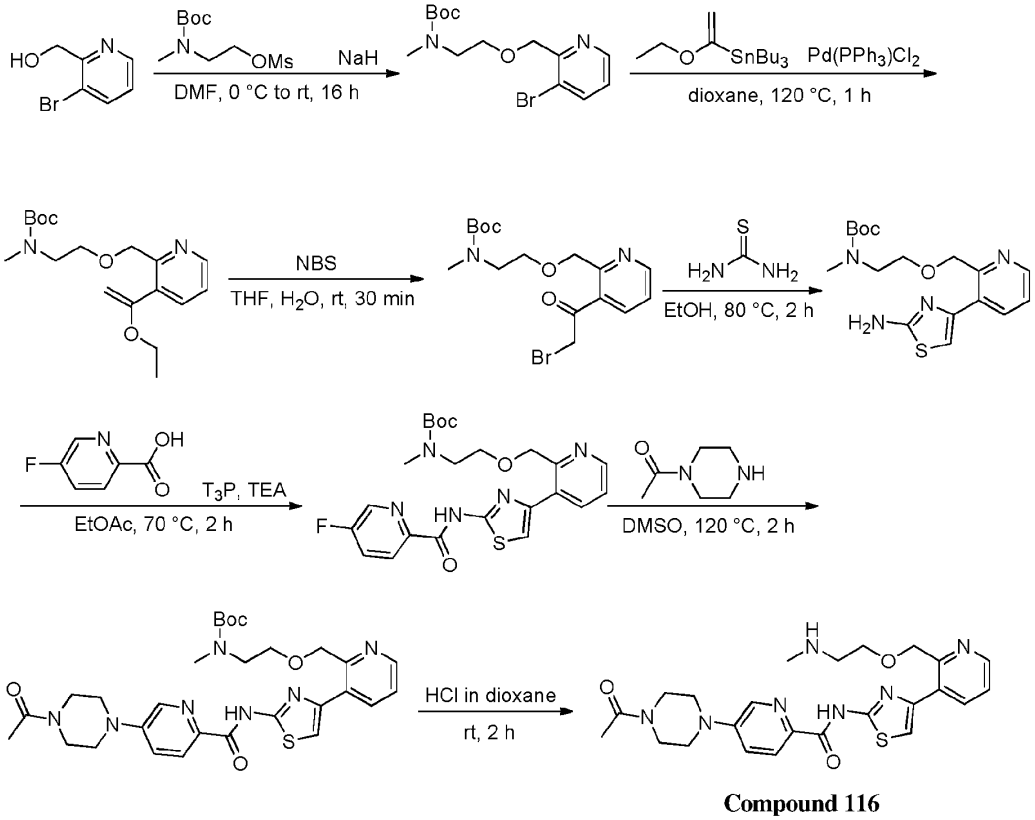
Synthesis of 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide (***Compound 108***)



[00305] To a stirred solution 5-fluoro-*N*-(4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide (50 mg, 0.13 mmol) in methanesulfinylmethane (3 mL) was added 1-(piperazin-1-yl)ethanone (83 mg, 0.65 mmol) at room temperature. The resulting mixture was stirred at 120 °C for 2 h. The mixture was allowed to cool down to room temperature. The reaction solution was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 33% to 38% B in 8 min, 38% B; Wave Length: 254 nm; RT1(min): 9; Number Of Runs: 0) nd concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-methoxyethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide as a white solid.

[00306] Yield 30 mg (47%). ^{1}1H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.56 (dd, J = 4.8, 1.6 Hz, 1H), 8.43 (d, J = 2.8 Hz, 1H), 8.15 (dd, J = 8.0, 1.6 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H), 7.54-7.45 (m, 2H), 4.72 (s, 2H), 3.66-3.59 (m, 6H), 3.51 (t, J = 5.2 Hz, 2H), 3.48-3.42 (m, 4H), 3.23 (s, 3H), 2.07 (s, 3H).m/z: [ESI$^+$] 497 (M + H)$^+$. ($C_{24}H_{28}N_6O_4S$)

***Experimental procedures* (*Compound 116*)**



Compound 116

Scheme 10. *Synthesis of* 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylamino)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide ((***Compound 116***)

Synthesis of tert-butyl (2-((3-bromopyridin-2-yl)methoxy)ethyl)(methyl)carbamate

[00307] A solution of (3-bromopyridin-2-yl)methanol (1.50 g, 7.97 mmol) in DMF (20 mL) was treated with NaH (0.50 g, 20.82 mmol) at 0 °C for 30 min, followed by the addition of *tert*-butyl *N*-[2-(methanesulfonyloxy)ethyl]-*N*-methylcarbamate (3.05 g, 12.04 mmol) in portions at 0 °C. The reaction was stirred at room temperature for 16 h. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (3 x 40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1) and concentrated under reduced pressure to afford *tert*-butyl (2-((3-bromopyridin-2-yl)methoxy)ethyl)(methyl)carbamate as a brown oil.

[00308] Yield 1.20 g (44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.4, 1H), 7.89 (d, *J* = 4.4 Hz, 1H), 7.15 (t, *J* = 4.8 Hz, 1H), 4.78 (s, 2H), 3.57 (t, *J* = 8.4 Hz, 2H), 3.49 (s, 3H), 3.44 (t, *J* = 8.4 Hz, 2H), 1.49 (s, 9H). m/z: [ESI$^+$] 345 $(M + H)^+$.

Synthesis of tert-butyl (2-((3-(1-ethoxyvinyl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate

[00309] A mixture of *tert*-butyl (2-((3-bromopyridin-2-yl)methoxy)ethyl)(methyl)carbamate (500 mg, 1.448 mmol), tributyl(1-ethoxyvinyl)stannane (790 mg, 2.187 mmol) and dichloropalladium; bis(triphenylphosphane) (150 mg, 0.214 mmol) in 1,4-dioxane (6 mL) was stirred at 120 °C for 1 h. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (50 mL). The combined organic layers were washed with brine (3 x 40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford *tert*-butyl (2-((3-(1-ethoxyvinyl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate as a brown oil.

[00310] Yield 400 mg (82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.8 Hz, 1H), 7.48 (d, *J* = 4.8 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 4.74 (s, 2H), 4.72-4.70 (m, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 3.78 (t, *J* = 8.4 Hz, 2H), 2.91 (s, 3H), 2.78 (t, *J* = 8.4 Hz, 2H), 1.45 (s, 9H), 1.17 (t, *J* = 4.8 Hz, 3H). m/z: [ESI$^+$] 337 $(M + H)^+$.

Synthesis of tert-butyl (2-((3-(2-bromoacetyl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate

[00311] A mixture of *tert*-butyl (2-((3-(1-ethoxyvinyl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate (400 mg, 1.189 mmol) ,NBS (260 mg, 1.461 mmol) and H_2O (0.20 mL) in THF (4 mL) was stirred at room temperature for 2 h. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford *tert*-butyl (2-((3-(2-bromoacetyl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate as a brown oil.

[00312] Yield 350 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.8 Hz, 1H), 7.48 (d, *J* = 4.8 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 3.46 (s, 2H), 3.01 (s, 2H), 2.79-2.70 (m, 4H), 1.68 (s, 3H), 1.41 (s, 9H). m/z: [ESI$^+$] 387 $(M + H)^+$.

Synthesis of tert-butyl (2-((3-(2-aminothiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate

[00313] A mixture of *tert*-butyl (2-((3-(2-bromoacetyl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate (350 mg, 0.904 mmol) and thiourea (350 mg, 4.598 mmol) in EtOH (4 mL) was stirred at 80 °C for 2 h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in Water (10mmol/L NH_4HCO_3), 40% to 60% gradient in 10 min; detector, UV 254 nm. Then concentrated under reduced pressure to afford *tert*-butyl (2-((3-(2-aminothiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate as a brown oil.

[00314] Yield 200 mg (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 4.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.06 (s, 1H), 6.95 (s, 2H), 4.76 (s, 2H), 3.73-3.45 (m, 4H), 2.89 (s, 3H), 1.45 (s, 9H) . m/z: [ESI^+] 365 $(M + H)^+$.

Synthesis of tert-butyl (2-((3-(2-(5-fluoropicolinamido)thiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate

[00315] A mixture of *tert*-butyl (2-((3-(2-aminothiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate (200 mg, 0.549 mmol), T_3P (450 mg, 1.414 mmol), triethylamine (0.3 mL) and 5-fluoropicolinic acid (700 mg, 4.961 mmol) in EtOAc (3 mL) was stirred at 70 °C for 2 h. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in Water (10mmol/L NH_4HCO_3), 50% to 60% gradient in 10 min; detector, UV 254 nm. the filtrate was concentrated under reduced pressure to afford *tert*-butyl (2-((3-(2-(5-fluoropicolinamido)thiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate as a brown oil.

[00316] Yield 120 mg (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.06 (s, 1H), 8.69-8.55 (m, 4H), 8.40 (t, J = 8.8 Hz, 1H), 8.30 (s, 1H), 7.68 (t, J = 8.8 Hz, 1H), 4.89 (s, 2H), 3.78-3.49 (m, 4H), 2.90 (s, 3H), 1.45 (s, 9H). m/z: [ESI^+] 488 $(M + H)^+$.

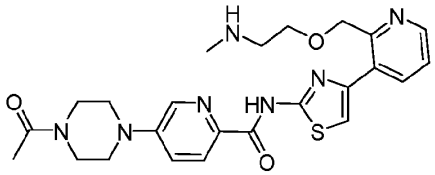
Synthesis of tert-butyl (2-((3-(2-(5-(4-acetylpiperazin-1-yl)picolinamido)thiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate

[00317] A solution of *tert*-butyl (2-((3-(2-(5-fluoropicolinamido)thiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate (120 mg, 0.246 mmol) and 1-(piperazin-1-yl)ethan-1-one (160 mg, 1.248 mmol) in DMSO (2 mL) was stirred at 120 °C for 2 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in Water (10mmol/L NH_4HCO_3), 50% to 60% gradient in 10 min; UV 254 nm. The resulting mixture was concentrated under reduced pressure to afford *tert*-butyl (2-((3-(2-(5-(4-acetylpiperazin-1-yl)picolinamido)thiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate as a brown oil.

[00318] Yield 80 mg (55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.75 (s, 1H), 8.30 (d, *J* = 2.8 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 7.60-7.57 (m, 2H), 7.32 (d, *J* = 2.8 Hz, 1H), 4.89 (s, 2H), 3.86-3.82 (m, 4H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.49 (s, 3H), 3.46 (t, *J* = 6.0 Hz, 2H), 2.92-2.99 (m, 4H), 2.20 (s, 3H), 1.62 (s, 9H). m/z: [ESI$^+$] 596 $(M + H)^+$.

Final Compounds

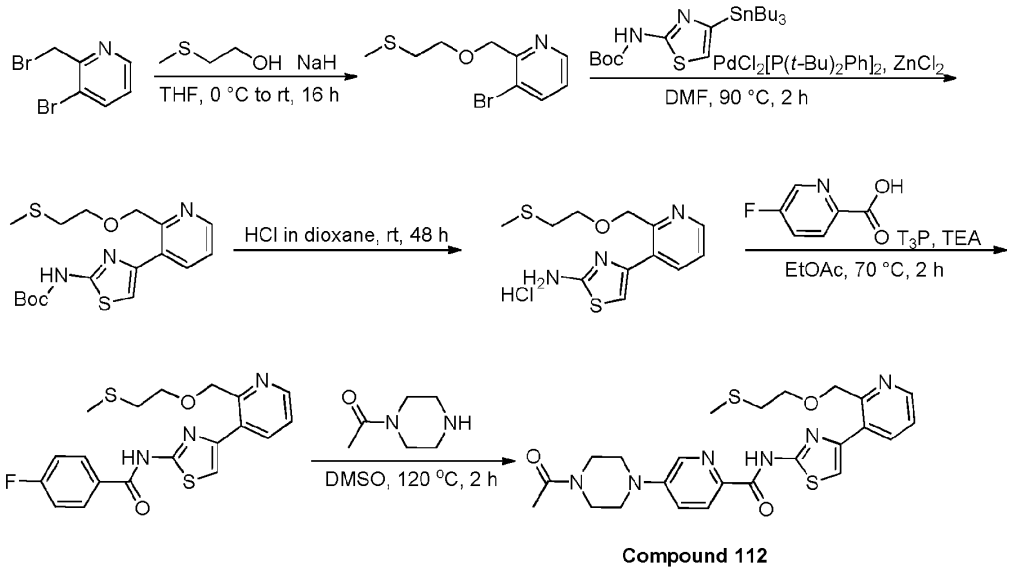
Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylamino)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide (***(Compound 116***)



[00319] A solution of *tert*-butyl (2-((3-(2-(5-(4-acetylpiperazin-1-yl)picolinamido)thiazol-4-yl)pyridin-2-yl)methoxy)ethyl)(methyl)carbamate (80 mg, 0.134 mmol) and HCl(gas) in 1,4-dioxane (3 mL, 98.738 mmol) in 1,4-dioxane (3 mL) was stirred at room temperature for 1 h.The mixturewas basified to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was concentrated under reduced pressure. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 27% B in 10 min, 27% B; Wave Length: 254 nm; RT1(min): 10; Number Of Runs: 0) and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylamino)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide as a white solid.

[00320] Yield 20 mg (30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.55-8.51 (m, 1H), 8.42-8.39 (m, 2H), 8.11-8.02 (m, 1H), 7.60 (s, 1H), 7.48-742 (m, 2H), 4.67 (s, 1H), 3.50 (s, 2H), 3.43-3.31 (m, 6H), 3.06 (s, 3H), 2.70-2.58 (m, 4H), 2.28 (t, *J* = 5.2 Hz, 2H), 2.06 (s, 3H). m/z: [ESI$^+$] 496 $(M + H)^+$. ($C_{22}H_{29}N_7O$).

Experimental procedures (Compound 112)



Compound 112

Scheme 11. *Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl) thiazol-2-yl)picolinamide (**Compound 112**)*

Synthesis of 3-bromo-2-((2-(methylthio)ethoxy)methyl)pyridine

[00321] To a solution of 2-(methylthio)ethanol (1.10 g, 11.957 mmol) in DMF (20 mL) was added NaH (0.38 g, 15.942 mmol) at 0 °C. The mixture was stirred for 15 min. 3-bromo-2-(bromomethyl)pyridine (2.00 g, 7.971 mmol) was added and the mixture was allowed to warm to RT and stirred for 1h.The mixture was basified to pH 8 with saturated NH_4Cl (aq.). The resulting mixture was extracted with EtOAc (100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1) to afford 3-bromo-2-((2-(methylthio)ethoxy)methyl)pyridine as a yellow oil.

[00322] Yield 1.00 g (48%). 1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.15 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.81 (s, 2H), 3.80 (t, *J* = 7.2 Hz, 2H), 2.79 (d, *J* = 7.2 Hz, 2H), 2.16 (s, 3H). m/z: [ESI$^+$] 262, 264 $(M+H)^+$

Synthesis of tert-butyl (4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)carbamate

[00323] To a stirred solution of 3-bromo-2-((2-(methylthio)ethoxy)methyl)pyridine (400 mg, 1.526 mmol) and *tert*-butyl *N*-[4-(tributylstannyl)-1,3-thiazol-2-yl]carbamate (1120 mg, 2.289 mmol) in DMF (5 mL) were added $ZnCl_2$ (208 mg, 1.526 mmol) and di-*tert*-butyl({dichloro[di-*tert*-butyl(phenyl)-lambda5-phosphanyl]palladio})phenyl-lambda5-phosphane (95 mg, 0.152 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. Desired product could be detected by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash

chromatography with the following conditions: Column, Spherical C18, 20 - 40 um,330; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B; (ACN); Flow rate: 80 mL/min; Gradient: 45%B - 65%B in 20 min; Detector, UV 254 nm. The fractions containing desired product were collected at 54% B and concentrated under reduced pressure to afford *tert*-butyl (4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)carbamate as a yellow solid.

[00324] Yield 260 mg (45%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.39 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.80 (s, 2H), 3.81 (*t*, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.14 (s, 3H), 1.56 (s, 9H). m/z: [ESI$^+$] 382,384 $(M+H)^+$

Synthesis of 4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine hydrochloride

[00325] A solution of *tert*-butyl (4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)carbamate (260 mg, 0.682 mmol) in 1,4-dioxane (3 mL, 98.738 mmol) was added 4 M HCl in dioxane (3 mL) dropwise at room temperature. The result mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to afford 4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine hydrochloride as an off-white solid.

[00326] Yield 180 mg (94%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.88 (d, *J* = 5.6 Hz, 1H), 8.73 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.12 (dd, *J* = 8.0, 5.6 Hz, 1H), 7.16 (s, 3H), 5.13 (s, 2H), 3.94 (t, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 6.4 Hz, 2H), 2.15 (s, 3H). m/z: [ESI$^+$] 282 $(M+H)^+$.

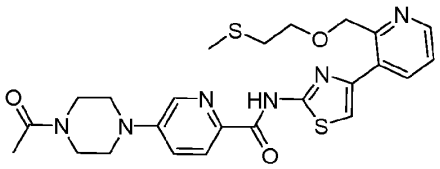
Synthesis of 4-fluoro-N-(4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)benzamide

[00327] To a stirred solution of 4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine hydrochloride (106 mg, 0.334 mmol) and 5-fluoropyridine-2-carboxylic acid (80 mg, 0.567 mmol) in EtOAc (1 mL) were added T_3P (271 mg, 0.852 mmol) and DIEA (110 mg, 0.851 mmol) dropwise at room temperature. The resulting mixture was stirred for 2 h at 70°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with the following conditions: Column, Spherical C18, 20 - 40 um,330; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B; (ACN); Flow rate: 80 mL/min; Gradient:45% B - 65% B in 20 min; Detector, UV 254 nm. The fractions containing desired product were collected at 54% B and concentrated under reduced pressure to afford 4-fluoro-*N*-(4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)benzamide as a yellow solid.

[00328] Yield 80 mg (52%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.05 (s, 1H), 8.66 (dd, *J* = 4.8, 2.8 Hz, 1H), 8.55 (d, *J* = 2.8 Hz, 1H), 8.40 (dd, *J* = 8.0, 4.8 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.72 - 7.63 (m, 2H), 7.50 - 7.42 (m, 1H), 4.88 (s, 2H), 3.85 (t, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 2.15 (s, 3H). m/z: [ESI$^+$] 404 $(M+H)^+$.

Final Compounds

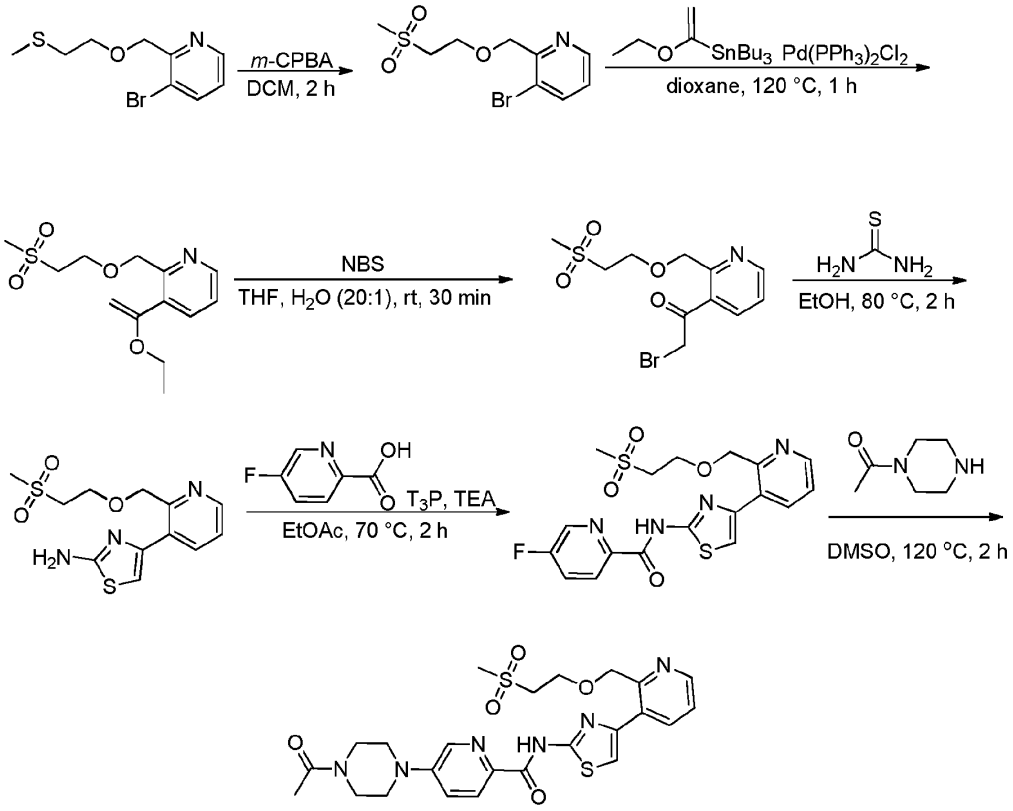
*Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide (**Compound 112**)*



[00329] A solution of 4-fluoro-*N*-(4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)benzamide (80 mg, 0.198 mmol) and 1-(piperazin-1-yl)ethanone (76 mg, 0.593 mmol) in DMSO (1 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere.The mixture was allowed to cool down to room temperature.The resulting mixture was concentrated under vacuum. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 52% B to 62% B in 10 min, 62% B; Wave Length: 254 nm; RT1 (min): 10; Number Of Runs: 0) to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylthio)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide as a white solid.

[00330] Yield 36 mg (36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.56 (dd, J = 4.8, 1.6 Hz, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.14 (dd, J = 8.0, 1.6 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.49 - 7.43 (m, 2H), 4.77 (s, 2H), 3.69 - 3.59 (m, 6H), 3.52 (d, J = 6.0 Hz, 2H), 3.45 (d, J = 6.0 Hz, 2H), 2.61 (t, J = 6.0 Hz, 3H), 2.10 - 2.05 (m, 5H). m/z: [ESI+] 513 $(M+H)^+$, ($C_{24}H_{28}N_6O_3S_2$).

Experimental procedures (Compound 113)



Scheme 12. *Synthesis of* 5-fluoro-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide ***(Compound 113)***

Synthesis of 3-bromo-2-((2-(methylsulfonyl)ethoxy)methyl)pyridine

[00331] A solution of 3-bromo-2-((2-(methylthio)ethoxy)methyl)pyridine (500 mg, 1.907 mmol) and *m*-CPBA (987 mg, 5.720 mmol) in DCM (5 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with the following conditions: Column, Spherical C18, 20 - 40 um, 330; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B; (ACN); Flow rate: 80 mL/min; Gradient: 40%B - 60%B in 20 min; Detector, UV 254 nm. The fractions containing desired product were collected at 54% B and concentrated under reduced pressure to afford 3-bromo-2-((2-(methylsulfonyl)ethoxy)methyl)pyridine as a yellow solid.

[00332] Yield 300 mg (53%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.19 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.83 (s, 2H), 4.11 - 4.04 (m, 2H), 3.30 (t, *J* = 6.0 Hz, 2H), 3.08 (s, 3H). m/z: [ESI$^+$] 294, 296 $(M+H)^+$

Synthesis of 3-(1-ethoxyvinyl)-2-((2-(methylsulfonyl)ethoxy)methyl)pyridine

[00333] To a stirred mixture of 3-bromo-2-((2-(methylsulfonyl)ethoxy)methyl)pyridine (300 mg, 1.020 mmol) and tributyl(1-ethoxyethenyl)stannane (552 mg, 1.528 mmol) in dioxane (3 mL) was added $Pd(PPh_3)_2Cl_2$ (72 mg, 0.103 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The mixture was basified to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3 x 50mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 3-(1-ethoxyvinyl)-2-((2-(methylsulfonyl)ethoxy)methyl)pyridine as a black oil.

[00334] Yield 260 mg (89%).1H NMR (400 MHz, Chloroform-*d*) δ 8.62 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.39 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.80 (s, 2H), 3.81 (t, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.14 (s, 3H), 1.56 (s, 9H). m/z: [ESI^+] 286 $(M+H)^+$

Synthesis of 2-bromo-1-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)ethan-1-one

[00335] A solution of 3-(1-ethoxyvinyl)-2-((2-(methylsulfonyl)ethoxy)methyl)pyridine (300 mg, 1.051 mmol) and NBS (281 mg, 1.579 mmol) in THF (3 mL) and H_2O (0.15 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under vacuum to afford 2-bromo-1-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)ethan-1-one (200 mg, 56.59%) as a black oil.

[00336] Yield 200 mg (57%). ^1H NMR (300 MHz, Chloroform-*d*) δ 7.76 - 7.63 (m, 1H), 7.63 - 7.35 (m, 2H), 5.11 - 3.69 (m, 1H), 2.78 (s, 3H), 1.82 - 1.79 (m, 4H), 1.73 - 1.70 (m, 2H). m/z: [ESI^+] 336 $(M+H)^+$

Synthesis of 4-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine

[00337] A solution of 2-bromo-1-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)ethan-1-one (200 mg, 0.595 mmol) and thiourea (91 mg, 1.195 mmol) in EtOH (2 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with the following conditions: Column, Spherical C18, 20 - 40 um, 330; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B; (ACN); Flow rate: 80 mL/min; Gradient: 45%B - 65%B in 20 min; Detector, UV 254 nm. The fractions containing desired product were collected at 54% B and concentrated under reduced pressure to afford 4-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine as a yellow solid.

[00338] Yield 150 mg (80%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.64 - 8.62 (m, 1H), 7.95 - 7.90 (m, 1H), 7.39 - 7.29 (m, 1H), 6.72 (s, 1H), 5.41 (s, 2H), 4.77 (s, 2H), 4.12 - 4.04 (m, 2H), 3.07 (s, 3H). m/z: [ESI^+] 313$(M+H)^+$

Synthesis of 5-fluoro-N-(4-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide

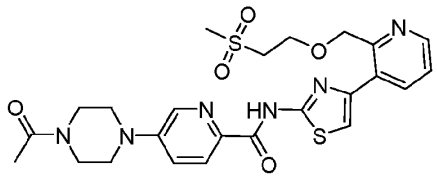
[00339] To a stirred solution of 4-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine (150 mg, 0.479 mmol) and5 -fluoropyridine-2-carboxylic acid (135 mg, 0.957 mmol) in EtOAc (2 mL) were added T_3P (457 mg, 1.436 mmol) and DIEA (186 mg, 1.439 mmol) dropwise at room temperature

under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 70°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with the following conditions: Column, Spherical C18, 20 - 40 um, 330; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B; (ACN); Flow rate: 80 mL/min; Gradient: 45%B - 65%B in 20 min; Detector, UV 254 nm. The fractions containing desired product were collected at 54% B and concentrated under reduced pressure to afford 5-fluoro-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide as a yellow solid.

[00340] Yield 100 mg (48%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 - 8.66 (m, 1H), 8.59 - 8.55 (m, 1H), 8.33 - 8.28 (m, 1H), 8.06 - 8.03 (m, 1H), 7.69 - 7.66 (m, 1H), 7.42 - 7.38 (m, 1H), 7.31 - 7.28 (m, 1H), 4.87 (s, 2H), 4.09 (t, *J* = 5.6 Hz, 2H), 3.31 (t, *J* = 5.6 Hz, 2H), 3.02 (s, 3H). m/z: [ESI$^+$] 437(M+H)$^+$

Final Compounds

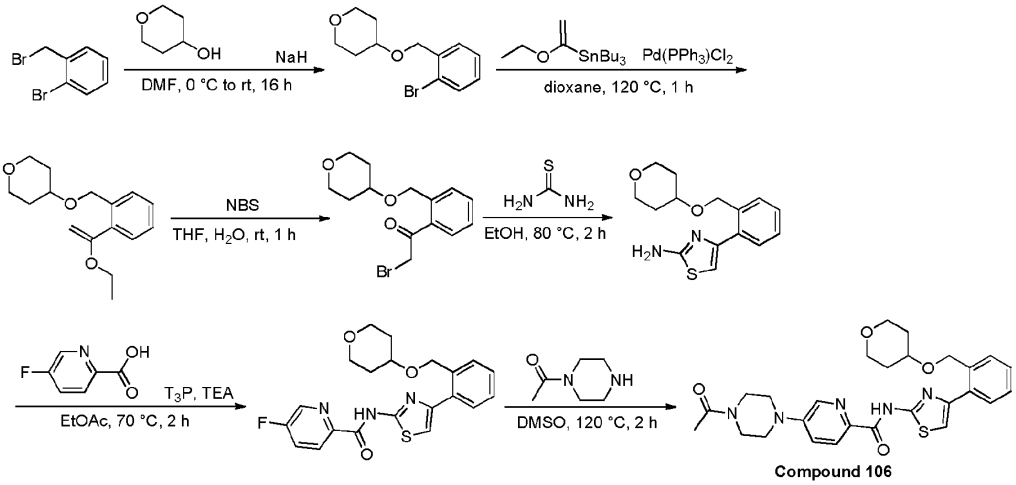
Synthesis of 5-fluoro-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide ***(Compound 113)***



[00341] A solution of 5-fluoro-*N*-(4-{2-[(2-methanesulfonylethoxy)methyl]pyridin-3-yl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (100 mg, 0.229 mmol) and 1-(piperazin-1-yl)ethanone (88 mg, 0.687 mmol) in DMSO (1 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 52% B to 62% B in 10 min, 62% B; Wave Length: 254 nm; RT1 (min): 10; Number Of Runs: 0) to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylsulfonyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide as a white solid.

[00342] Yield 30 mg (24%). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 11.73 (br s, 1H), 8.60 - 8.56 (m, 1H), 8.45 - 8.42 (m, 1H), 8.15 - 8.12 (m, 1H), 8.05 - 8.01 (m, 1H), 7.60 (s, 1H), 7.53 - 7.45 (m, 2H), 4.82 (s, 2H), 3.87 (t, *J* = 5.6 Hz, 2H), 3.71 - 3.54 (m, 4H), 3.54 - 3.48 (m, 2H), 3.48 - 3.40 (m, 2H), 3.37 (t, *J* = 5.6 Hz, 2H), 2.91 (s, 3H), 2.06 (s, 3H). m/z: [ESI+] 545 (M+H)$^+$, ($C_{24}H_{28}N_6O_5S_2$).

Experimental procedures (Compound 106)



Scheme 13. *Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-{2-[(oxan-4-yloxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (**Compound 106**)*

Synthesis of 4-((2-bromobenzyl)oxy)tetrahydro-2H-pyran

[00343] To a stirred solution of oxan-4-ol (1.23 g, 12.003 mmol) in DMF (20 mL) was added NaH (0.64 g, 16.004 mmol) in portions at 0 °C. The resulting mixture was stirred for 30min at 0 °C under nitrogen atmosphere. To the above mixture was added 1-bromo-2-(bromomethyl)benzene (2.00 g, 8.002 mmol) in DMF (20 mL) dropwise over 2 min at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (1 x 150 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% - 30% ethyl acetate in petroleum ether and concentrated under reduced pressure to afford 4-[(2-bromophenyl)methoxy]oxane (1.60 g, 73%) as a light yellow oil. Yield 1.60 g (60%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 - 7.52 (m, 2H), 7.45 - 7.31 (m, 1H), 7.25 - 7.12 (m, 1H), 4.64 (s, 2H), 4.07 - 3.93 (m, 2H), 3.74 - 3.62 (m, 1H), 3.55 - 3.44 (m, 2H), 2.10 - 1.92 (m, 2H), 1.85 - 1.64 (m, 2H). No MS signal.

Synthesis of 4-((2-(1-ethoxyvinyl)benzyl)oxy)tetrahydro-2H-pyran

[00344] To a stirred solution of 4-[(2-bromophenyl)methoxy]oxane (1.60 g, 5.901 mmol) and tributyl(1-ethoxyethenyl)stannane (3.20 g, 8.851 mmol) in dioxane (30 mL) was added $Pd(PPh_3)_2Cl_2$ (0.41 g, 0.590 mmol) in portions at room temperature. The resulting mixture was stirred for 1 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 4-{[2-(1-ethoxyethenyl)phenyl]methoxy}oxane (1.50 g, 96%) as a brown oil.

[00345] Yield 1.50 g (97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.45 (m, 1H), 7.40 - 7.32 (m, 2H), 7.28 - 7.24 (m, 1H), 4.67 (s, 2H), 4.32 (d, J = 2.0 Hz, 1H), 4.26 (d, J = 2.0 Hz, 1H), 4.03 - 3.95 (m, 2H), 3.91 (q, J = 7.2 Hz, 2H), 3.64 - 3.54 (m, 1H), 3.53 - 3.41 (m, 2H), 2.01 - 1.88 (m, 2H), 1.75 - 1.65 (m, 2H), 1.13 (t, J = 7.2 Hz, 3H).

m/z: [ESI$^+$] 263 $(M+H)^+$

Synthesis of 2-bromo-1-(2-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)phenyl)ethan-1-one

[00346] To a stirred solution of 4-{[2-(1-ethoxyethenyl)phenyl]methoxy}oxane (1.60 g, 6.099 mmol) in THF (30 mL) and water (2 mL) was added NBS (1.19 g, 6.709 mmol) in portions at room temperature. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (1 x 150 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-bromo-1-{2-[(oxan-4-yloxy)methyl]phenyl}ethanone (1.60 g, 83%) as a brown oil.

[00347] Yield 1.60 g (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 - 7.49 (m, 2H), 7.49 - 7.33 (m, 2H), 4.82 (s, 2H), 4.50 (s, 2H), 4.00 - 3.94 (m, 2H), 3.69 - 3.56 (m, 1H), 3.54 - 3.43 (m, 2H), 2.06 - 1.85 (m, 2H), 1.62 - 1.57 (m, 2H). m/z: [ESI$^+$] 313, 315 $(M+H)^+$

Synthesis of 4-(2-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)phenyl)thiazol-2-amine

[00348] To a stirred solution of 2-bromo-1-{2-[(oxan-4-yloxy)methyl]phenyl}ethanone (1.50 g, 4.789 mmol) in EtOH (30 mL) was added thiourea (0.55 g, 7.183 mmol) in portions at room temperature. The resulting mixture was stirred for 1 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with sat. $NaHCO_3$ (50 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% - 70% ethyl acetate in petroleum ether and concentrated under reduced pressure to afford 4-{2-[(oxan-4-yloxy)methyl]phenyl}-1,3-thiazol-2-amine (1.00 g, 72%) as a light yellow solid.

[00349] Yield 1.00 g (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.53 (m, 1H), 7.54 - 7.45 (m, 1H), 7.33 - 7.29 (m, 2H), 6.99 (br s, 2H), 6.70 (s, 1H), 4.67 (s, 2H), 3.89 - 3.71 (m, 2H), 3.66 - 3.47 (m, 1H), 3.39 - 3.32 (m, 2H), 1.96 - 1.79 (m, 2H), 1.55 - 1.35 (m, 2H).

m/z: [ESI$^+$] 291 $(M+H)^+$

Synthesis of 5-fluoro-N-(4-(2-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)phenyl)thiazol-2-yl)picolinamide

[00350] To a stirred solution of 4-{2-[(oxan-4-yloxy)methyl]phenyl}-1,3-thiazol-2-amine (500 mg, 1.722 mmol), TEA (500 mg, 4.941 mmol) and 5-fluoropyridine-2-carboxylic acid (480 mg, 3.402 mmol) in EtOAc (15 mL) was added T_3P (3.29 g, 5.166 mmol) dropwise at room temperature. The resulting mixture was stirred for 2 h at 70 °C under a nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (1 x 50 mL), dried

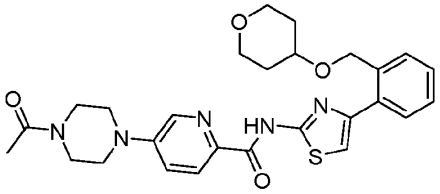
over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% - 70% ethyl acetate in petroleum ether and concentrated under reduced pressure to afford 5-fluoro-*N*-(4-{2-[(oxan-4-yloxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (600 mg, 84%) as a light yellow oil.

[00351] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (br s, 1H), 8.87 - 8.74 (m, 1H), 8.39 - 8.25 (m, 1H), 8.13 - 7.99 (m, 1H), 7.74 - 7.62 (m, 1H), 7.62 - 7.53 (m, 1H), 7.53 - 7.45 (m, 1H), 7.45 - 7.33 (m, 2H), 4.74 (s, 2H), 3.84 - 3.69 (m, 2H), 3.69 - 3.49 (m, 1H), 3.32 - 3.31 (m, 2H), 1.94 - 1.62 (m, 2H), 1.61 - 1.19 (m, 2H).

m/z: [ESI$^+$] 414 $(M+H)^+$

Final Compounds

*Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-{2-[(oxan-4-yloxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (**Compound 106**)*

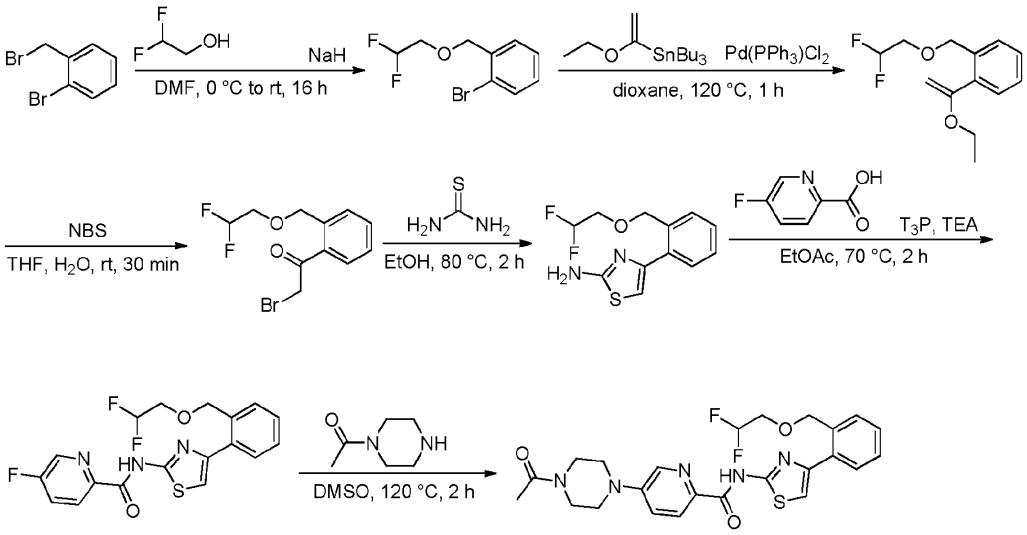


[00352] To a stirred solution of 5-fluoro-*N*-(4-{2-[(oxan-4-yloxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (300 mg, 0.726 mmol) in DMSO (10 mL) was added 1-(piperazin-1-yl)ethanone (450 mg, 3.511 mmol) dropwise at room temperature. The resulting mixture was stirred for 1hat 120 °C under a nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction solution was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 330 g; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 20% B - 40% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected at 30% B and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-{2-[(oxan-4-yloxy)methyl]phenyl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (200 mg, 53%) as a light yellow solid.

[00353] Yield 200 mg (53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (br s, 1H), 8.42 (d, J = 2.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.67 - 7.62 (m, 1H), 7.60 - 7.53 (m, 1H), 7.50 (dd, J = 2.8, 8.8 Hz, 1H), 7.41 (s, 1H), 7.40 - 7.34 (m, 2H), 4.71 (s, 2H), 3.91 - 3.70 (m, 2H), 3.69 - 3.52 (m, 5H), 3.54 - 3.48 (m, 2H), 3.47 - 3.35 (m, 2H), 3.35 - 3.24 (m, 2H), 2.06 (s, 3H), 1.94 - 1.72 (m, 2H), 1.51 - 1.36 (m, 2H).

m/z: [ESI$^+$] 522 $(M+H)^+$, ($C_{27}H_{31}N_5O_4S$).

Experimental procedures (Compound 107)



Compound 107

Scheme 14. *Synthesis of* 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2,2-difluoroethoxy)methyl)phenyl)thiazol-2-yl)picolinamide ***(Compound 107)***

Synthesis of 1-bromo-2-[(2,2-difluoroethoxy)methyl]benzene

[00354] To a stirred mixture of 2,2-difluoroethanol (1.31 g, 16.004 mmol) in DMF (20 mL) was added NaH (0.29 g, 12.003 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added 1-bromo-2-(bromomethyl)benzene (2.00 g, 8.002 mmol) in portions over 5 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-30% methanol in dichloromethane to afford 1.20 g of 1-bromo-2-[(2,2-difluoroethoxy)methyl]benzene as a light yellow oil.

[00355] Yield 1.20 g (60%). ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 5.97 (tt, J = 55.6, 4.0 Hz, 1H), 4.72 (s, 2H), 3.90 - 3.77 (m, 2H). m/z: [ESI$^+$] 251, 253 $(M + H)^+$.

Synthesis of 1-((2,2-difluoroethoxy)methyl)-2-(1-ethoxyvinyl)benzene

[00356] To a stirred mixture of 1-bromo-2-[(2,2-difluoroethoxy)methyl]benzene (1.20 g, 4.780 mmol) and tributyl(1-ethoxyethenyl)stannane (2.07 g, 5.736 mmol) in dioxane (10 mL) was added $Pd(PPh_3)_2Cl_2$ (0.67 g, 0.955 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room

temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 200 mL) . The combined organic layers were washed with water (3 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 850 mg of 1-((2,2-difluoroethoxy)methyl)-2-(1-ethoxyvinyl)benzene as a light yellow oil.

[00357] Yield 850 mg (73%). ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.76 - 7.63 (m, 1H), 7.61 - 7.35 (m, 2H), 7.34 - 7.25 (m, 1H), 5.97 (tt, J = 55.6, 4.0 Hz, 1H), 4.72 (s, 2H), 4.30 - 4.18 (m, 2H), 3.90 - 3.77 (m, 2H), 3.51 - 3.17 (m, 2H), 1.28 - 1.18 (m, 3H). m/z: [ESI$^+$] 243 $(M + H)^+$.

Synthesis of 2-bromo-1-(2-((2,2-difluoroethoxy)methyl)phenyl)ethan-1-one

[00358] A mixture of 1-[(2,2-difluoroethoxy)methyl]-2-(1-ethoxyethenyl)benzene (850 mg, 3.509 mmol) and NBS (937 mg, 5.264 mmol) in THF (20 mL) and H_2O (1 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 300 mL). The combined organic layers were washed with water (3 x 300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 800 mg of 2-bromo-1-(2-((2,2-difluoroethoxy)methyl)phenyl)ethan-1-one as a yellow oil.

[00359] Yield 1.00 g (98%). ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.78 - 7.65 (m, 1H), 7.64 - 7.36 (m, 3H), 5.96 (tt, J = 55.6, 4.0 Hz, 1H), 5.02 - 4.61 (m, 2H), 4.48 (s, 2H), 3.99 - 3.61 (m, 2H). m/z: [ESI$^+$] 293, 295 $(M + H)^+$.

Synthesis of 4-(2-((2,2-difluoroethoxy)methyl) phenyl)thiazol-2-amine

[00360] A mixture of 2-bromo-1-(2-((2,2-difluoroethoxy)methyl)phenyl)ethan-1-one (1.00 g, 3.412 mmol) and thiourea (0.39 g, 5.118 mmol) in EtOH (10 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% - 30% methanol in dichloromethane to afford 800 mg 4-(2-((2,2-difluoroethoxy)methyl) phenyl)thiazol-2-amine as a yellow oil.

[00361] Yield 800 mg (87%). m/z: [ESI$^+$] 271 $(M + H)^+$.

Synthesis of N-(4-(2-((2,2-difluoroethoxy) methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide

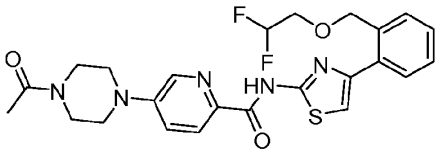
[00362] To a stirred mixture of 4-(2-((2,2-difluoroethoxy)methyl) phenyl)thiazol-2-amine (300 mg, 1.110 mmol) and T_3P (1.06 g, 3.328 mmol) in ethyl acetate (5 mL) were added 5-fluoropyridine-2-carboxylic acid (313 mg, 2.218 mmol) and TEA (337 mg, 3.330 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. Desired

product could be detected by LCMS. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford 300 mg of *N*-(4-(2-((2,2-difluoroethoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide as a light yellow oil.

[00363] Yield 300 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 8.57 (d, J = 2.8 Hz, 1H), 8.39 (dd, J = 8.8, 4.4 Hz, 1H), 7.76 - 7.61 (m, 2H), 7.60 - 7.50 (m, 1H), 7.55 - 7.38 (m, 2H), 7.27 (s, 1H), 5.96 (tt, J = 55.6, 4.0 Hz, 1H), 4.79 (s, 2H), 3.78 - 3.72 (m, 2H). m/z: [ESI$^+$] 394 $(M + H)^+$.

Final Compounds

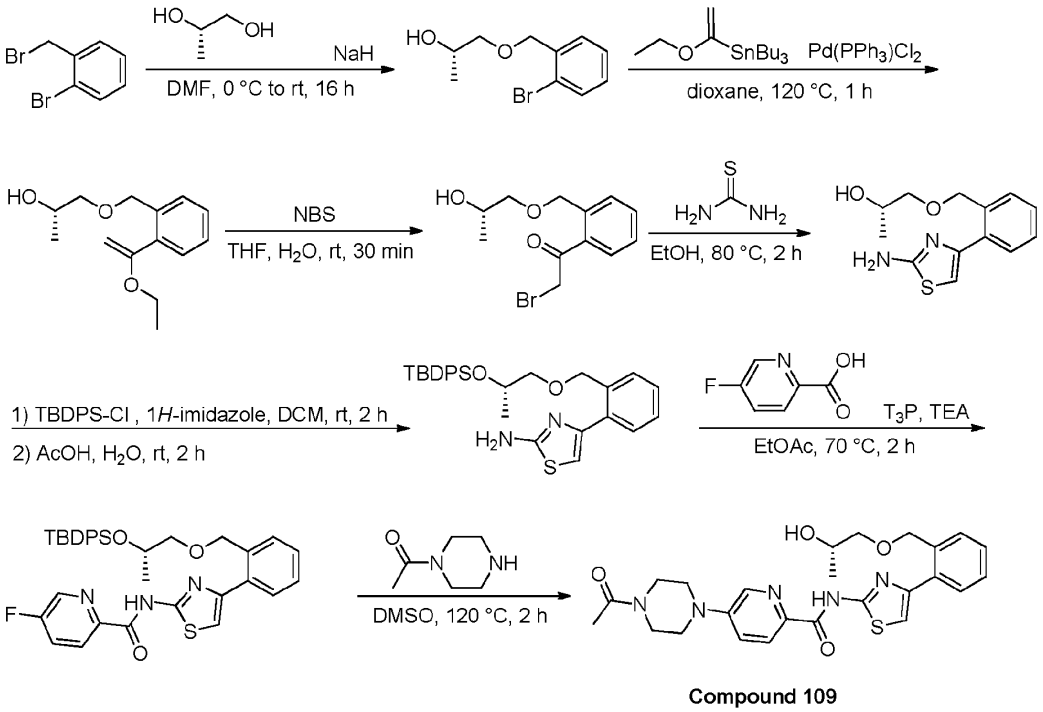
Synthesis of 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2,2-difluoroethoxy)methyl)phenyl)thiazol-2-yl)picolinamide ***(Compound 107)***



[00364] A mixture of *N*-(4-(2-((2,2-difluoroethoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide (300 mg, 0.763 mmol) and 1-(piperazin-1-yl)ethanone (391 mg, 3.051 mmol) in DMSO (3 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 120 g; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 50% B - 70% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected at 60% B and concentrated under reduced pressure to afford 130 mg of 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2,2-difluoroethoxy)methyl)phenyl)thiazol-2-yl)picolinamide as a white solid.

[00365] Yield 130 mg (34%). ^{1}H NMR (400 MHz, DMSO) δ 8.43 (d, J = 2.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.79 - 7.63 (m, 1H), 7.57 - 7.50 (m, 2H), 7.46 - 7.35 (m, 3H), 6.24 - 6.18 (m, 1H), 4.83 (s, 2H), 3.81 - 3.76 (m, 2H), 3.63 (dd, J = 6.8, 3.8 Hz, 4H), 3.50 - 3.46 (m, 4H), 2.07 (s, 3H). m/z: [ESI$^+$] 502 $(M + H)^+$.

Experimental procedures (Compound 109)



Compound 109

Scheme 15. *Synthesis of* (*S*)-5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-hydroxypropoxy)methyl) phenyl) thiazol-2-yl)picolinamide ***(Compound 109)***

Synthesis of (2*S*)-1-[(2-bromophenyl)methoxy]propan-2-ol

[00366] To a stirred mixture of 1-bromo-2-(bromomethyl)benzene (5.00 g, 20.005 mmol) in DMF (50 mL) was added NaH (0.72 g, 30.008 mmol) in portions at 0 °C under nitrogen atmosphere. To the above mixture was added (*S*)-1,2-propanediol (3.04 g, 40.010 mmol) in portions over 2 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200mL). The resulting mixture was extracted with ethyl acetate (4 x 100 mL). The combined organic layers were washed with water (4 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2.30 g of (2*S*)-1-[(2-bromophenyl)methoxy]propan-2-ol as a light yellow oil.

[00367] Yield 2.30 g (47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0, 1.2 Hz, 1H), 7.54 - 7.43 (m, 1H), 7.40 - 7.30 (m, 1H), 7.25 - 7.13 (m, 1H), 4.65 (d, J = 1.6 Hz, 2H), 4.25 - 3.99 (m, 1H), 3.58 (dd, J = 9.6, 3.2 Hz, 1H), 3.40 (dd, J = 9.6, 8.0 Hz, 1H). m/z: [ESI$^+$] 245, 247 $(M + H)^+$.

Synthesis of (*S*)-1-((2-(1-ethoxyvinyl)benzyl)oxy)propan-2-ol

[00368] To a stirred mixture of (2*S*)-1-[(2-bromophenyl)methoxy]propan-2-ol (1.00 g, 4.080 mmol) and tributyl(1-ethoxyethenyl)stannane (1.77 g, 4.896 mmol) in dioxane (10 mL) was added $Pd(PPh_3)_2Cl_2$ (0.57

g, 0.816 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 800 mg of (*S*)-1-((2-(1-ethoxyvinyl)benzyl)oxy)propan-2-ol as a light yellow oil.

Yield 800 mg (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 - 7.21 (m, 4H), 4.76 - 4.72 (m, 2 H), 4.32 - 4.28 (m, 2H), 3.99 - 3.60 (m, 5 H), 1.37 - 1.29 (m, 3 H), 0.95 - 0.85 (m, 3 H). m/z: [ESI$^+$] 237 $(M + H)^+$.

Synthesis of (*S*)-2-bromo-1-(2-((2-hydroxypropoxy)methyl)phenyl)ethan-1-one

[00369] A mixture of (*S*)-1-((2-(1-ethoxyvinyl)benzyl)oxy)propan-2-ol (700 mg, 2.962 mmol) and NBS (791 mg, 4.444 mmol) in THF (7 mL) and H_2O (1 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 700 mg of (*S*)-2-bromo-1-(2-((2-hydroxypropoxy)methyl)phenyl)ethan-1-one as a light yellow oil.

[00370] Yield 700 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.64 (m, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.56 - 7.32 (m, 2H), 4.91 (s, 2H), 4.75 - 4.49 (m, 2H), 3.94 - 3.64 (m, 3H), 0.95 - 0.85 (m, 3 H). m/z: [ESI$^+$] 287 $(M + H)^+$.

Synthesis of (*S*)-1-((2-(2-aminothiazol-4-yl)benzyl)oxy)propan-2-ol

[00371] A mixture of (*S*)-2-bromo-1-(2-((2-hydroxypropoxy)methyl)phenyl)ethan-1-one (700 mg, 2.438 mmol) and thiourea (278 mg, 3.652 mmol) in EtOH (10 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL) . The combined organic layers were washed with water (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-30% methanol in dichloromethane to afford 500 mg of (*S*)-1-((2-(2-aminothiazol-4-yl)benzyl)oxy)propan-2-ol as a yellow oil.

[00372] Yield 500 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.68 (m, 2H), 7.45 - 7.32 (m, 3H), 4.53 (s, 2H), 4.10 - 3.95 (m, 1H), 3.79 - 3.39 (m, 1H), 3.45 - 2.98 (m, 1H), 1.22 - 1.06 (m, 3H). m/z: [ESI$^+$] 265 $(M + H)^+$.

Synthesis of (*S*)-4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-amine

[00373] To a stirred mixture of (*S*)-1-((2-(2-aminothiazol-4-yl)benzyl)oxy)propan-2-ol (500 mg, 1.892 mmol) and 1*H*-imidazole (193 mg, 2.835 mmol) in DCM (8 mL) was added TBDPS-Cl (780 mg, 2.838 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2

h at room temperature under nitrogen atmosphere. To the above mixture was added AcOH (2 mL) in portions over 2 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (2 x 100 mL) . The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% ethyl acetate in petroleum ether to afford 800 mg of (*S*)-4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-amine as a yellow oil.

[00374] Yield 800 mg (84%). m/z: [ESI$^+$] 503 $(M + H)^+$.

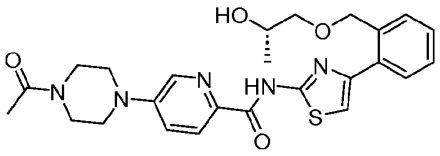
Synthesis of (*S*)-*N*-(4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide

[00375] To a stirred mixture of (*S*)-4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-amine (600 mg, 1.193 mmol) and T_3P (1.14 g, 3.580 mmol) in EtOH (10 mL) were added 5-fluoropyridine-2-carboxylic acid (336 mg, 2.381 mmol) and TEA (362 mg, 3.577 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The residue was purified by silica gel column chromatography, eluted with 1%-6% methanol in dichloromethane to afford 440 mg of (*S*)-*N*-(4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamid as a yellow oil.

[00376] Yield 440 mg (59%). m/z: [ESI$^+$] 626 $(M + H)^+$.

Final Compounds

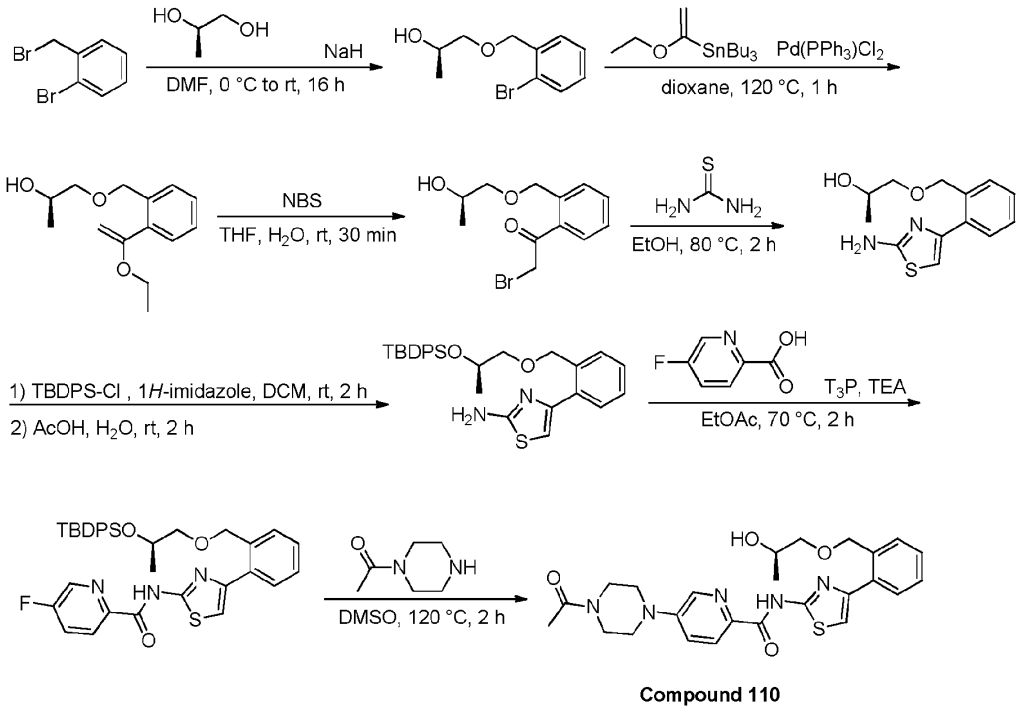
Synthesis of (*S*)-5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-hydroxypropoxy)methyl)phenyl)thiazol-2-yl)picolinamide ***(Compound 109)***



[00377] A mixture of (*S*)-*N*-(4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamid (440 mg, 0.703 mmol) and 1-(piperazin-1-yl)ethanone (360 mg, 2.809 mmol) in DMSO (7 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 330 g; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 20% B - 40% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected at 30% B and concentrated under reduced pressure to afford 10 mg (*S*)-5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-hydroxypropoxy)methyl)phenyl)thiazol-2-yl)picolinamide as a white solid.

[00378] Yield 500 mg (78%). Yield 10 mg (3%). ^{1}H NMR (400 MHz, DMSO) δ 11.59 (s, 1H), 8.43 (d, J = 2.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.85 - 7.62 (m, 1H), 7.69 - 7.45 (m, 2H), 7.45 - 7.25 (m, 2H), 4.65 (dd, J = 8.4, 4.0 Hz, 3H), 3.81 - 3.76 (m, 1H), 3.70 - 3.45 (m, 5H), 3.44 (s, 5H), 2.07(s, 3H), 1.04 (d, J = 6.4 Hz, 3H). m/z: [ESI$^+$] 496 (M + H)$^+$.

Experimental procedures (Compound 110)



Scheme 16. *Synthesis of* (*R*)-5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-hydroxypropoxy)methyl) phenyl) thiazol-2-yl)picolinamide ***(Compound 110)***

Synthesis of (*R*)-1-((2-bromobenzyl)oxy)propan-2-ol

[00379] A solution of *R*-1,2-propanediol (3.04 g, 40.010 mmol) in DMF (50 mL) was treated with NaH (0.72 g, 30.008 mmol) for 30 min at 0 °C under nitrogen atmosphere followed by the addition of 1-bromo-2-(bromomethyl)benzene (5.00 g, 20.005 mmol) dropwise at room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (300 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-30% methanol in dichloromethane to afford 3.70 g of (2*R*)-1-[(2-bromophenyl)methoxy]propan-2-ol as a yellow oil.

[00380] Yield 3.70 g (75%). m/z: [ESI$^+$] 245, 247 (M + H)$^+$.

Synthesis of (*R*)-1-((2-(1-ethoxyvinyl)benzyl)oxy)propan-2-ol

[00381] To a stirred mixture of (2*R*)-1-[(2-bromophenyl)methoxy]propan-2-ol (3.00 g, 12.239 mmol) and tributyl(1-ethoxyethenyl)stannane (6.60 g, 18.275 mmol) in dioxane (30 mL) was added $Pd(PPh_3)_2Cl_2$ (1.72 g, 2.448 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 90 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2.30 g of (*R*)-1-((2-(1-ethoxyvinyl)benzyl)oxy)propan-2-ol as a yellow oil.

[00382] Yield 2.30 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.59 (m, 1H), 7.47 - 7.43 (m, 1H), 7.41 - 7.33 (m, 2H), 4.72 - 4.63 (m, 2H), 4.29 (dd, J = 25.6, 2.4 Hz, 2H), 3.97 - 3.84 (m, 2H), 3.54 - 3.34 (m, 1H), 3.27 (dd, J = 9.6, 8.4 Hz, 1H), 2.54 (d, J = 2.8 Hz, 1H), 1.28 - 1.18 (m, 3H), 1.02 - 0.90 (m, 3H). m/z: [ESI$^+$] 237 $(M + H)^+$.

Synthesis of (*R*)-2-bromo-1-(2-((2-hydroxypropoxy)methyl)phenyl)ethan-1-one

[00383] A mixture of (*R*)-1-((2-(1-ethoxyvinyl)benzyl)oxy)propan-2-ol (2.30 g, 9.733 mmol) and NBS (2.60 g, 14.600 mmol) in THF (10 mL) and H_2O (1 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (300 mL). The combined organic phase was washed with brine (3 x 100 mL), dried with Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford 1.10 g of (*R*)-2-bromo-1-(2-((2-hydroxypropoxy)methyl)phenyl)ethan-1-one as a yellow oil.

[00384] Yield 1.10 g (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.56 (m, 1H), 7.50 - 7.32 (m, 2H), 7.35 - 7.10 (m, 1H), 4.73 - 4.55 (m, 2H), 4.19 -3.74 (m, 2H), 3.71 - 3.40 (m, 2H), 3.42 - 3.11 (m, 1H), 1.02 - 0.90 (m, 3H). m/z: [ESI$^+$] 287, 289 $(M + H)^+$.

Synthesis of (*R*)-1-((2-(2-aminothiazol-4-yl)benzyl)oxy)propan-2-ol

[00385] A mixture of (*R*)-2-bromo-1-(2-((2-hydroxypropoxy)methyl)phenyl)ethan-1-one (1.10 g, 3.818 mmol) and thiourea (0.44 g, 5.780 mmol) in EtOH (10 mL) was stirred for 1 h at 80 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford 360 mg of (*R*)-1-((2-(2-aminothiazol-4-yl)benzyl)oxy)propan-2-ol as a light yellow solid.

[00386] Yield 1.10 g (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.51 (m, 1H), 7.51 - 7.39 (m, 1H), 7.40 - 7.22 (m, 2H), 5.50 - 5.35 (m, 1H), 4.51 (s, 2H), 4.14 - 3.94 (m, 2H), 3.73 -3.46 (m, 1H), 1.27 - 0.98 (m, 3H). m/z: [ESI$^+$] 265 $(M + H)^+$.

Synthesis of (*R*)-4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-amine

[00387] To a stirred mixture of (*R*)-1-((2-(2-aminothiazol-4-yl)benzyl)oxy)propan-2-ol (360 mg, 1.362 mmol) and TBDPS-Cl (1122 mg, 4.082 mmol) in DCM (5 mL) was added 1*H*-imidazole (185 mg, 2.717 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford 500 mg of (*R*)-4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-amine as a yellow oil.

[00388] Yield 500 mg (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 - 7.85 (m, 1H), 7.82 - 7.63 (m, 4H), 7.62 - 7.52 (m, 2H), 7.50 (dd, J = 7.2, 4.4 Hz, 1H), 7.49 - 7.40 (m, 3H), 7.44 - 7.29 (m, 3H), 7.32 - 7.18 (m, 1H), 4.34 (s, 2H), 3.99 - 3.83 (m, 2H), 3.73 -3.46 (m, 1H), 1.10 (s, 9H), 1.27 - 0.98 (m, 3H). m/z: [ESI$^+$] 503 $(M + H)^+$.

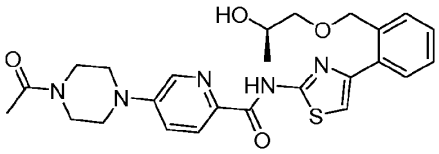
Synthesis of (R)-N-(4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide

[00389] To a stirred mixture of (*R*)-4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-amine (500 mg, 0.995 mmol) and T_3P (946 mg, 2.973 mmol) in EtOAc (9 mL) were added 5-fluoropyridine-2-carboxylic acid (277 mg, 1.963 mmol) and TEA (302 mg, 2.984 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 70 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-60% methanol in dichloromethane to afford 160 mg of (*R*)-*N*-(4-(2-((2-((*tert*-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide as a light yellow oil.

[00390] Yield (160 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.8 Hz, 1H), 8.37 (dd, J = 8.8, 4.4 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.72 - 7.64 (m, 4H), 7.56 - 7.43 (m, 2H), 7.41 - 7.32 (m, 9H), 4.46 (s, 2H), 3.73 - 3.46 (m, 1H), 3.44 - 3.37 (m, 2H), 1.12 - 1.05 (m, 9H), 0.96 - 0.76 (m, 3H). m/z: [ESI$^+$] 626 $(M + H)^+$.

Final Compounds

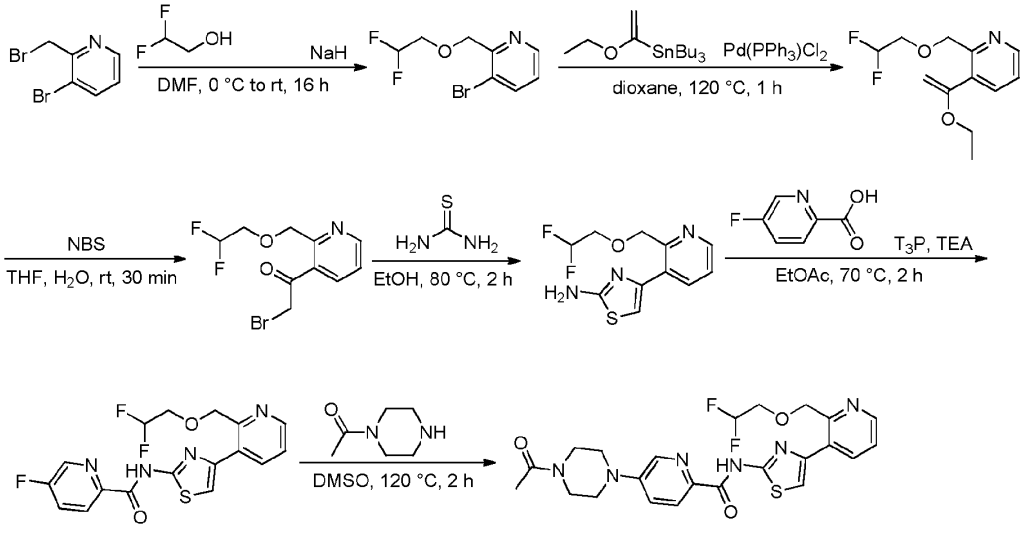
Synthesis of (*R*)-5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-hydroxypropoxy)methyl)phenyl)thiazol-2-yl)picolinamide ***(Compound 110)***



[00391] A mixture of (*R*)-*N*-(4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)phenyl)thiazol-2-yl)-5-fluoropicolinamide (160 mg, 0.256 mmol) and 1-(piperazin-1-yl)ethanone (131 mg, 1.022 mmol) in DMSO (3 mL) was stirred for 1 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To the above mixture was added triethylamine trihydrofluoride (1 mL, 0.006 mmol) dropwise over 1 min at room temperature. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 330 g; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 40% B - 60% B in 20 min; Detector: 254 nm. The fractions containing desired product were collected at 50% B and concentrated under reduced pressure to afford 68 mg of (*R*)-5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-hydroxypropoxy)methyl)phenyl)thiazol-2-yl)picolinamide as a white solid.

[00392] Yield 68 mg (55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.43 (d, J = 2.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.85 - 7.43 (m, 4H), 7.39 (dd, J = 5.6, 3.2 Hz, 2H), 4.68 -4.63 (m, 2H), 3.80 - 3.72 (m, 1H), 3.68 - 3.59 (m, 5H), 3.56 - 3.31 (m, 5H), 2.07 (s, 3H), 1.04 (d, J = 6.4 Hz, 3H). m/z: [ESI$^+$] 496 $(M + H)^+$.

Experimental procedures (Compound 111)



Compound 111

Scheme 17. *Synthesis of* 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2,2-difluoroethoxy)methyl)pyridin-3-yl) thiazol-2-yl)picolinamide ***(Compound 111)***

Synthesis of 3-bromo-2-((2,2-difluoroethoxy)methyl)pyridine

[00393] To a stirred mixture of 2,2-difluoroethanol (1.96 g, 23.912 mmol) in DMF (30 mL) was added NaH (0.43 g, 17.934 mmol) in portions at 0 °C under nitrogen atmosphere. To the above mixture was added 3-bromo-2-(bromomethyl)pyridine (3.00 g, 11.956 mmol) in portions over 2 min at room temperature. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was monitored by LCMS. After the reaction was completed, the reaction was quenched by the addition of water (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (1 x 300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1% to 70% methanol in dichloromethane to afford 3-bromo-2-[(2,2-difluoroethoxy)methyl]pyridine (1.50 g, 49.77%) as a light yellow oil.

[00394] Yield (1.50 g, 50%) ^{1}H NMR (400 MHz, CCl_3) δ 8.59 (dd, J = 4.8, 1.6 Hz, 1H), 7.92 (dd, J = 8.0, 1.6 Hz, 1H), 7.19 (dd, J = 8.0, 4.8 Hz, 1H), 5.92-5.74 (m, 1H), 4.89 (s, 2H), 3.86-3.83 (m, 2H).

Synthesis of 2-((2,2-difluoroethoxy)methyl)-3-(1-ethoxyvinyl)pyridine

[00395] To a stirred mixture of 3-bromo-2-[(2,2-difluoroethoxy)methyl]pyridine (1.30 g, 5.158 mmol) and tributyl(1-ethoxyethenyl)stannane (7.45 g, 20.632 mmol) in dioxane (10 mL) was added $Pd(PPh_3)_2Cl_2$ (0.72 g, 1.032 mmol, 0.2 equiv) in portions at 90 °C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, and quenched by the addition of water (50 mL). The reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used to next step without further purification.

Synthesis of 2-bromo-1-(2-((2,2-difluoroethoxy)methyl)pyridin-3-yl)ethan-1-one

[00396] A mixture of 2-[(2,2-difluoroethoxy) ethyl]-3-(1-ethoxyethenyl) yridine (1.35 g, 5.550 mmol) and NBS (1.98 g, 11.100 mmol) in 11 mL mix solvents of THF and water (10/1) was stirred at room temperature for 30 min under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was quenched by the addition of water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used to the next step directly without further purification.

Synthesis of 4-(2-((2,2-difluoroethoxy)methyl)pyridin-3-yl)thiazol-2-amine

[00397] A mixture of 2-bromo-1-{2-[(2,2-difluoroethoxy)methyl]pyridin-3-yl}ethanone (1.50 g, 5.100 mmol) and thiourea (0.78 g, 10.200 mmol) in EtOH (10 mL, 172.133 mmol) was stirred at 80 °C for 16 h

under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. After the reaction was completed, the reaction mixture was dried under reduced pressure and the residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford 4-{2-[(2,2-difluoroethoxy)methyl]pyridin-3-yl}-1,3-thiazol-2-amine (700 mg, 50%) as a yellow solid.

[00398] Yield (700 mg, 51%) ^{1}H NMR (400 MHz,CCl_3) δ 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.06 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.36 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.97 (s, 1H), 6.06-5.75 (m, 1H), 4.99 (s, 2H), 4.93 (s, 2H), 3.86-3.83 (m, 2H).

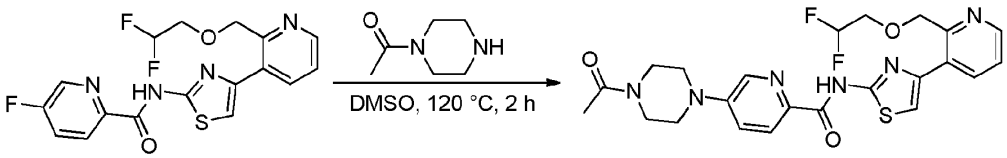
Synthesis of N-(4-(2-((2,2-difluoroethoxy)methyl)pyridin-3-yl)thiazol-2-yl)-5-fluoropicolinamide

[00399] To a stirred mixture of 4-{2-[(2,2-difluoroethoxy)methyl]pyridin-3-yl}-1,3-thiazol-2-amine (700 mg, 2.580 mmol) and T_3P (2.46 g, 7.738 mmol) in EtOAc (10 mL) were added 5-fluoropyridine-2-carboxylic acid (728 mg, 5.159 mmol) and TEA (783 mg, 7.738 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the resulting mixture was quenched by the addition of water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford *N*-(4-{2-[(2,2-difluoroethoxy)methyl]pyridin-3-yl}-1,3-thiazol-2-yl)-5-fluoropyridine-2-carboxamide (700 mg, 68%) as a yellow solid.

[00400] Yield (700 mg, 69%). ^{1}H NMR (400 MHz, CCl_3) δ 11.05 (s, 1H), 8.67 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.58 - 8.48 (m, 1H), 8.45 - 8.26 (m, 1H), 8.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.68-7.62 (m, 1H), 7.59 – 7.40 (m, 2H), 5.95-5.91 (m, 1H), 4.94 (s, 2H), 3.89-3.81 (m, 2H).

Final Compounds

Synthesis of 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2,2-difluoroethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide ***(Compound 111)***



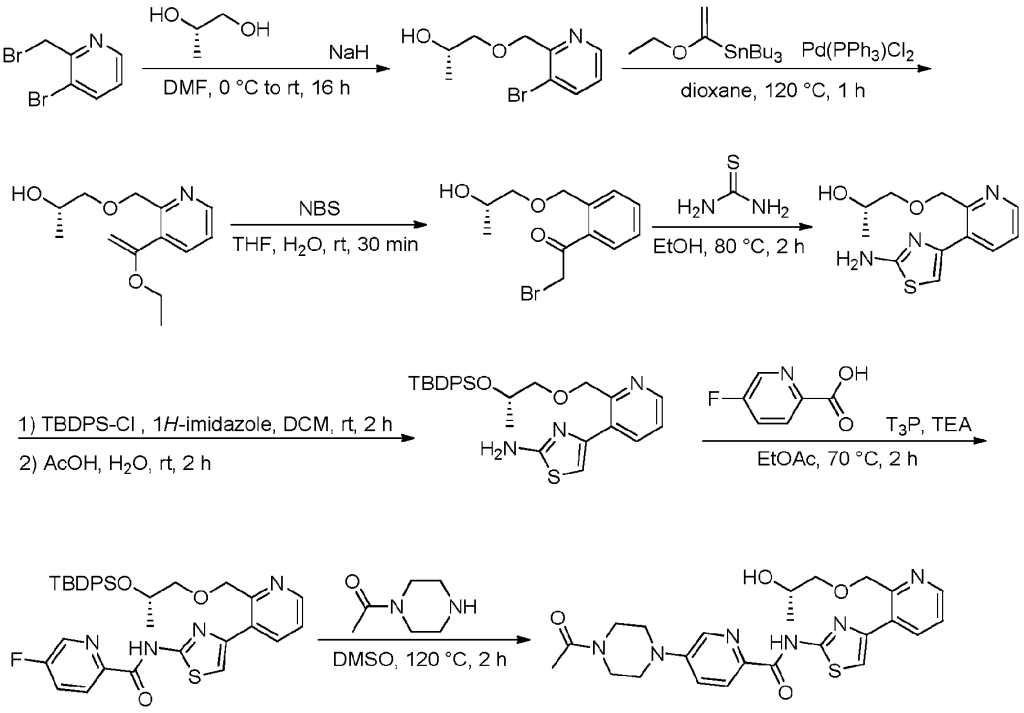
Compound 111

[00401] A mixture of *N*-(4-{2-[(2,2-difluoroethoxy)methyl]pyridin-3-yl}-1,3-thiazol-2-yl)-5-fluoropyridine-2-carboxamide (300 mg, 0.761 mmol) and 1-(piperazin-1-yl)ethanone (117 mg, 0.913 mmol) in DMSO (3 mL) was stirred at 120 °C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the mixture was allowed to cool down to room temperature. The mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 120 g; Mobile Phase A: water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 60 mL/min. The fractions containing desired product were collected and

concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-{2-[(2,2-difluoroethoxy)methyl]pyridin-3-yl}-1,3-thiazol-2-yl)pyridine-2-carboxamide (108 mg, 28%) as a white solid.

[00402] Yield (108 mg, 28%). ^{1}H NMR (400 MHz, DMSO) δ11.70 (s, 1H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.43 (d, *J* = 2.8 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.56 (s, 1H), 7.51-7.48 (m, 2H), 6.15-6.12 (m, 1H), 4.91 (s, 2H), 3.81-3.78 (m, 2H), 3.64-3.59 (m, 4H), 3.54 – 3.42 (m, 4H), 2.07 (s, 3H).

Experimental procedures (Compound 114)



Compound 114

Scheme 18. *Synthesis of* (S)-5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-hydroxypropoxy)methyl)pyridin-3-yl) thiazol-2-yl)picolinamide ***(Compound 114)***

Synthesis of (S)-1-((3-bromopyridin-2-yl)methoxy)propan-2-ol

[00403] To a stirred mixture of (S)-1,2-propanediol (1.21 g, 15.942 mmol) in DMF (20 mL) was added NaH (0.29 g, 11.957 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h under nitrogen atmosphere. To the above mixture was added 3-bromo-2-(bromomethyl)pyridine (2.00 g, 7.971 mmol) in dropwise for over 2 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by LCMS. After the reaction was completed, the reaction was quenched by the addition of water (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with

water (1 x 300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford (2*S*)-1-[(3-bromopyridin-2-yl)methoxy]propan-2-ol (700 mg, 35%) as a yellow oil.

[00404] Yield (700 mg, 36%) ^{1}H NMR(400 MHz, Chloroform-d) δ 8.56 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.17 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.10 - 4.78 (m, 2H), 4.07 - 4.03 (m, 1H), 3.99 - 3.50 (m, 1H), 3.43-3.41 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H).

Synthesis of (S)-1-((3-(1-ethoxyvinyl)pyridin-2-yl)methoxy)propan-2-ol

[00405] To a stirred mixture of (2*S*)-1-[(3-bromopyridin-2-yl)methoxy]propan-2-ol (700 mg, 2.844 mmol) and tributyl(1-ethoxyethenyl)stannane (4109 mg, 11.377 mmol) in dioxane (10 mL) was added $Pd(PPh_3)_2Cl_2$ (399 mg, 0.568 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 90 °C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the reaction was quenched by the addition of water (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried under vacumn and used to next step without further purification.

Synthesis of (S)-2-bromo-1-(2-((2-hydroxypropoxy)methyl)pyridin-3-yl)ethan-1-one

[00406] A mixture of (S)-1-((3-(1-ethoxyvinyl)pyridin-2-yl)methoxy)propan-2-ol (700 mg, 2.949 mmol) and NBS (630 mg, 3.539 mmol) in 11 mL mix solvents of THF and water (10/1) was stirred at room temperature for 30 min under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was quenched by the addition of water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used to the next step directly without further purification.

Synthesis of (S)-1-((3-(2-aminothiazol-4-yl)pyridin-2-yl)methoxy)propan-2-ol

[00407] A mixture of 2-bromo-1-(2-{[(2*S*)-2-hydroxypropoxy]methyl}pyridin-3-yl)ethanone (1.20 g, 4.165 mmol) and thiourea (1268 mg, 16.658 mmol) in EtOH (10 mL) was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried under vacumn and purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford (2*S*)-1-{[3-(2-amino-1,3-thiazol-4-yl)pyridin-2-yl]methoxy}propan-2-ol (250 mg, 32% over 3 steps) as a yellow oil.

Synthesis of (S)-4-(2-((2-((*tert*-butyldiphenylsilyl)oxy)propoxy)methyl)pyridin-3-yl)thiazol-2-amine

[00408] To a stirred mixture of (2*S*)-1-{[3-(2-amino-1,3-thiazol-4-yl)pyridin-2-yl]methoxy}propan-2-ol (250 mg, 0.942 mmol) and TBDPS-Cl (0.39 g, 1.413 mmol) in DCM (5 mL) was added 1H-imidazole

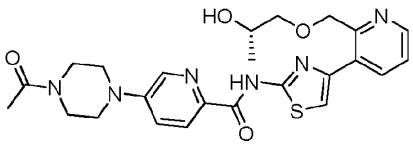
(0.096 g, 1.413 mmol, 1.5 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford 1-tert-butyl-*N*-[4-(2-{[(2S)-2-[(tert-butyldiphenylsilyl)oxy]propoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-yl]-1,1-diphenylsilanamine (240 mg, 50%) as a yellow oil.

Synthesis of S)-N-(4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)pyridin-3-yl)thiazol-2-yl)-5-fluoropicolinamide

[00409] To a stirred mixture of 4-(2-{[(2S)-2-[(tert-butyldiphenylsilyl)oxy]propoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-amine (240 mg, 0.476 mmol) and T_3P (455 mg, 1.430 mmol) in EA (5 mL) were added 5-fluoropyridine-2-carboxylic acid (134 mg, 0.950 mmol) and TEA (145 mg, 1.433 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the resulting mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 80 g; Mobile Phase A: water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 60 mL/min. The fractions containing desired product were collected and concentrated under reduced pressure to afford *N*-[4-(2-{[(2S)-2-[(tert-butyldiphenylsilyl)oxy]propoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-yl]-5-fluoropyridine-2-carboxamide (240 mg, 82%) as a yellow oil.

Final Compounds

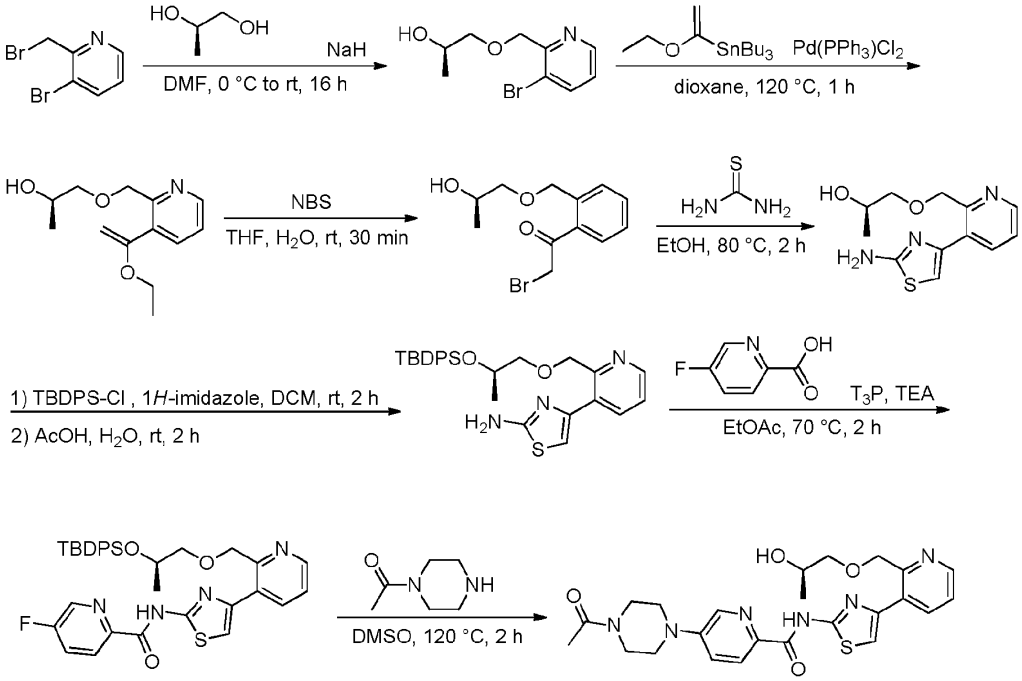
Synthesis of (S)-5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-hydroxypropoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide ***(Compound 114)***



[00410] A mixture of *N*-[4-(2-{[(2S)-2-[(tert-butyldiphenylsilyl)oxy]propoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-yl]-5-fluoropyridine-2-carboxamide (240 mg, 0.391 mmol) and 1-(piperazin-1-yl)ethanone (97 mg, 0.757 mmol) in DMSO (4 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To the above mixture was added triethylamine trihydrofluoride (1 mL, 0.006 mmol, 0.02 equiv) dropwise over 1 min at room temperature. The resulting mixture was stirred for additional 16 h at room temperature. The reaction was monitored by LCMS. The mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 80 g; Mobile Phase A: water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 60 mL/min. The fractions containing desired product were collected and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-[4-(2-{[(2*S*)-2-hydroxypropoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-yl]pyridine-2-carboxamideas (17.0 mg) as a light yellow solid.

[00411] ^{1}H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 8.55 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.43 (d, *J* = 3.2 Hz, 1H), 8.15 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 7.59 - 7.29 (m, 2H), 4.84 - 4.56 (m, 3H), 3.74 - 3.71 (m, 1H), 3.63 - 3.61 (m, 3H), 3.50 - 3.35 (m, 7H), 0.97 (d, *J* = 6.4 Hz, 3H).

***Experimental procedures* (*Compound 115*)**



Compound 115

Scheme 19. *Synthesis of* (*R*)-5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-hydroxypropoxy)methyl)pyridin-3-yl) thiazol-2-yl)picolinamide (***Compound 115***)

Synthesis of (*R*)-1-((3-bromopyridin-2-yl) methoxy)propan-2-ol

[00412] To a stirred mixture of (*R*)-1,2-propanediol (1.21 g, 15.942 mmol) in DMF (20 mL) was added NaH (0.29 g, 11.957 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h under nitrogen atmosphere. To the above mixture was added 3-bromo-2-(bromomethyl)pyridine (2.00 g, 7.971 mmol) in dropwise for over 2 min at room temperature. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by LCMS. After the reaction was completed, the reaction was quenched by the addition of water (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (1 x 300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford (2*R*)-1-[(3-bromopyridin-2-yl)methoxy]propan-2-ol (700 mg, 35%) as a yellow oil.

[00413] Yield (700 mg, 36%) ^{1}H NMR(400 MHz, Chloroform-d) δ 8.56 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.17 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.10 - 4.78 (m, 2H), 4.07 - 4.03 (m, 1H), 3.99 - 3.50 (m, 1H), 3.43-3.41 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H).

Synthesis of (R)-1-((3-(1-ethoxyvinyl)pyridin-2-yl)methoxy)propan-2-ol

[00414] To a stirred mixture of (2*R*)-1-[(3-bromopyridin-2-yl)methoxy]propan-2-ol (700 mg, 2.844 mmol) and tributyl(1-ethoxyethenyl)stannane (4109 mg, 11.377 mmol) in dioxane (10 mL) was added $Pd(PPh_3)_2Cl_2$ (399 mg, 0.568 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 90 °C for 1 h under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the reaction was quenched by the addition of water (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried under vacumn and used to next step without further purification.

Synthesis of (*R*)-2-bromo-1-(2-((2-hydroxypropoxy)methyl)pyridin-3-yl)ethan-1-one

[00415] A mixture of (*R*)-1-((3-(1-ethoxyvinyl)pyridin-2-yl)methoxy)propan-2-ol (700 mg, 2.949 mmol) and NBS (630 mg, 3.539 mmol) in 11 mL mix solvents of THF and water (10/1) was stirred at room temperature for 30 min under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was quenched by the addition of water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used to the next step directly without further purification.

Synthesis of (R)-1-((3-(2-aminothiazol-4-yl)pyridin-2-yl)methoxy)propan-2-ol

[00416] A mixture of 2-bromo-1-(2-{[(2*R*)-2-hydroxypropoxy]methyl}pyridin-3-yl)ethanone (1.20 g, 4.165 mmol) and thiourea (1268 mg, 16.658 mmol) in EtOH (10 mL) was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried under vacumn and purified by silica gel column chromatography, eluted with 1%-70% methanol in dichloromethane to afford (2*R*)-1-{[3-(2-amino-1,3-thiazol-4-yl)pyridin-2-yl]methoxy}propan-2-ol (250 mg, 32% over 3 steps) as a yellow oil.

Synthesis of (*R*)-4-(2-((2-((tert-butyldiphenylsilyl)oxy) propoxy)methyl)pyridin-3-yl)thiazol-2-amine

To a stirred mixture of (2*R*)-1-{[3-(2-amino-1,3-thiazol-4-yl)pyridin-2-yl]methoxy}propan-2-ol (250 mg, 0.942 mmol) and TBDPS-Cl (0.39 g, 1.413 mmol) in DCM (5 mL) was added 1H-imidazole (0.096 g, 1.413 mmol, 1.5 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 1%-70% methanol in

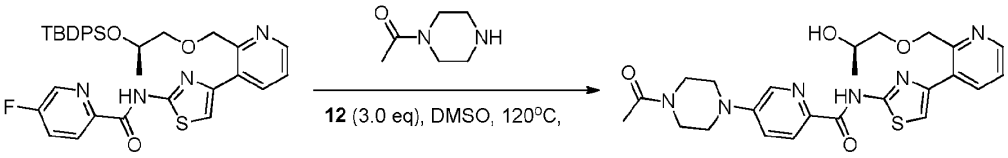
dichloromethane to afford 1-tert-butyl-*N*-[4-(2-{[(2*R*)-2-[(tert-butyldiphenylsilyl)oxy]propoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-yl]-1,1-diphenylsilanamine (240 mg, 50%) as a yellow oil.

Synthesis of (*R*)-N-(4-(2-((2-((tert-butyldiphenylsilyl)oxy)propoxy)methyl)pyridin-3-yl)thiazol-2-yl)-5-fluoropicolinamide

[00417] To a stirred mixture of 4-(2-{[(2*R*)-2-[(tert-butyldiphenylsilyl)oxy]propoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-amine (240 mg, 0.476 mmol) and T_3P (455 mg, 1.430 mmol) in EA (5 mL) were added 5-fluoropyridine-2-carboxylic acid (134 mg, 0.950 mmol) and TEA (145 mg, 1.433 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. After the reaction was completed, the resulting mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 80 g; Mobile Phase A: water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 60 mL/min. The fractions containing desired product were collected and concentrated under reduced pressure to afford *N*-[4-(2-{[(2*R*)-2-[(tert-butyldiphenylsilyl)oxy]propoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-yl]-5-fluoropyridine-2-carboxamide (240 mg, 82%) as a yellow oil.

Final Compounds

Synthesis of (*R*)-5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-hydroxypropoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide **(Compound 115)**

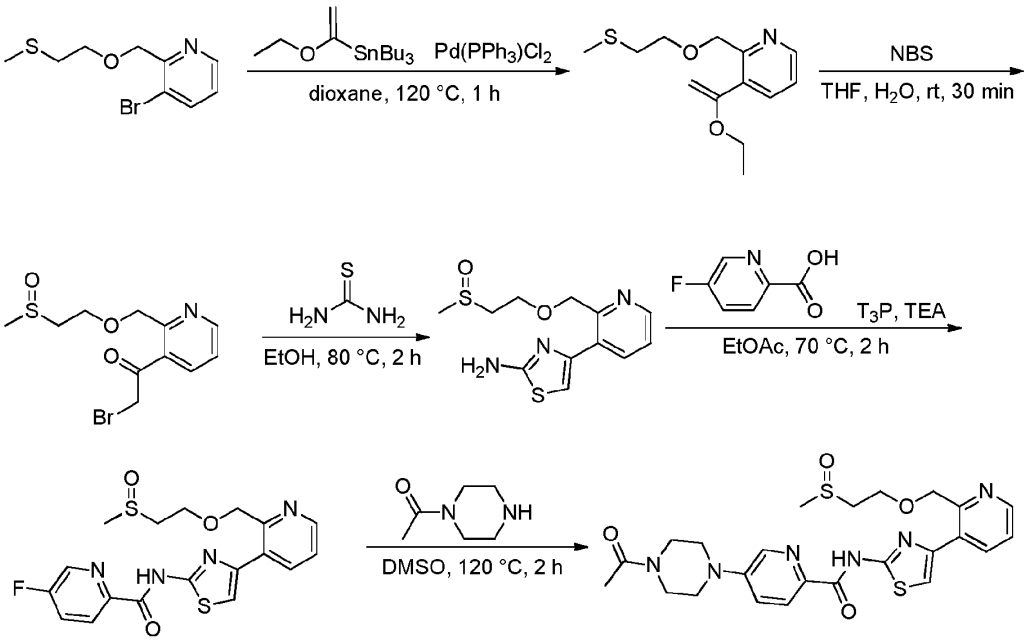


Compound 115

[00418] A mixture of *N*-[4-(2-{[(2R)-2-[(tert-butyldiphenylsilyl)oxy]propoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-yl]-5-fluoropyridine-2-carboxamide (240 mg, 0.391 mmol) and 1-(piperazin-1-yl)ethanone (97 mg, 0.757 mmol) in DMSO (4 mL) was stirred for 2 h at 120 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To the above mixture was added triethylamine trihydrofluoride (1 mL, 0.006 mmol, 0.02 equiv) dropwise over 1 min at room temperature. The resulting mixture was stirred for additional 16 h at room temperature. The reaction was monitored by LCMS. The mixture was purified by reverse phase flash chromatography with the following conditions: Column: Spherical C18, 20 - 40 um, 80 g; Mobile Phase A: water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 60 mL/min. The fractions containing desired product were collected and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-[4-(2-{[(2*R*)-2-hydroxypropoxy]methyl}pyridin-3-yl)-1,3-thiazol-2-yl]pyridine-2-carboxamideas (18.0 mg) as a light yellow solid.

[00419] ^{1}H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 8.55 (dd, J = 4.8, 1.6 Hz, 1H), 8.43 (d, J = 3.2 Hz, 1H), 8.15 (dd, J = 8.0, 1.6 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.70 (s, 1H), 7.59 - 7.29 (m, 2H), 4.84 - 4.56 (m, 3H), 3.74 - 3.71 (m, 1H), 3.63 - 3.61 (m, 3H), 3.50 - 3.35 (m, 7H), 0.97 (d, J = 6.4 Hz, 3H).

Experimental procedures **(Compound 117)**



Compound 117

Scheme 20. *Synthesis of* 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylsulfinyl)ethoxy) methyl) pyridin-3-yl)thiazol-2-yl)picolinamide **(Compound 117)**

Synthesis of 3-(1-ethoxyvinyl)-2-((2-(methylthio)ethoxy)methyl)pyridine

[00420] To a stirred solution of 3-bromo-2-((2-(methylthio)ethoxy)methyl)pyridine (2.00 g, 7.629 mmol) and tributyl(1-ethoxyethenyl)stannane (4.13 g, 11.444 mmol) in dioxane (20 mL) was added $Pd(PPh_3)_2Cl_2$ (0.54 g, 0.763 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 120 °C for 16 h under nitrogen atmosphere. After the reaction was completed, the mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with the following conditions: Column, Spherical C18, 20 - 40 um,330; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 80 mL/min. The fractions containing desired product were collected and concentrated under reduced pressure to afford 3-(1-ethoxyvinyl)-2-((2-(methylthio)ethoxy)methyl)pyridine as a yellow oil.

[00421] Yield 1.30 g (67%). ^{1}H NMR (300 MHz, Chloroform-d) δ 8.59 (dd, J = 4.8, 1.6 Hz, 1H), 7.71 - 7.68 (m, 1H), 7.23 – 7.21 (m, 1H), 4.75 (s, 2H), 4.39 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.93 (q, J = 7.2 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.13 (s, 3H), 0.95 (s, 3H). m/z: [ESI$^+$] 254 $(M+H)^+$

Synthesis of 2-bromo-1-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)ethan-1-one

[00422] A mixture of 3-(1-ethoxyvinyl)-2-((2-(methylthio)ethoxy)methyl)pyridine (1.30 g, 5.131 mmol) and NBS (1.37 g, 7.697 mmol) in THF (13 mL) and H_2O (0.5 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. After the reaction was completed, the resulting mixture was quenched by addition of water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-bromo-1-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)ethan-1-one (1.00 g, 60%) as a yellow oil.

[00423] Yield 1.00 g (60%). ^{1}H NMR (300 MHz, Chloroform-d) δ 8.73 - 8.56 (m, 1H), 7.75 - 7.63 (m, 1H), 7.53 - 7.43 (m, 1H), 4.99 - 4.82 (m, 1H), 4.00 - 3.85 (m, 1H), 3.78 - 3.63 (m, 1H), 2.75 (s, 3H), 2.65 - 2.61 (m, 2H), 2.13 (s, 1H). m/z: [ESI$^+$] 320 $(M+H)^+$

Synthesis of 4-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine

[00424] A solution of 2-bromo-1-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)ethan-1-one (1.00 g, 3.123 mmol) and thiourea (0.48 g, 6.246 mmol) in EtOH (10 mL) was stirred at 80 °C for 2 h under nitrogen atmosphere. After the reaction was completed, the mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with the following conditions: Column, Spherical C18, 20 - 40 um,330; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 80 mL/min. The fractions containing desired product were collected and concentrated under reduced pressure to afford 4-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine as a yellow solid.

[00425] Yield 300 mg (32%). ^{1}H NMR (300 MHz, Chloroform-d) δ 8.62 (dd, J = 4.8, 1.6 Hz, 1H), 7.99 (dd, J = 8.0, 1.6 Hz, 1H), 7.37 (dd, J = 8.0, 4.8 Hz, 1H), 6.81 (s, 1H), 6.12 (s, 2H), 4.87 - 4.72 (m, 2H), 4.17 - 4.01 (m, 2H), 3.13-3.11 (m, 1H), 3.03 - 2.87 (m, 1H), 2.66 (s, 3H). m/z: [ESI$^+$] 298 $(M+H)^+$

Synthesis of 5-fluoro-N-(4-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide

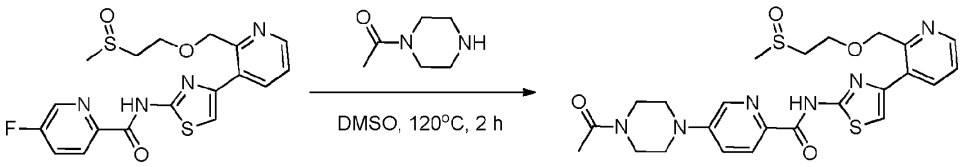
[00426] To a stirred solution of 4-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-amine (300 mg, 1.009 mmol) and 5-fluoropyridine-2-carboxylic acid (285 mg, 2.020 mmol) in EtOAc (3 mL) were added T_3P (963 mg, 3.027 mmol) and DIEA (391 mg, 3.025 mmol) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 70 °C for 2 h under nitrogen atmosphere. After the reaction was completed, the mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with the following conditions: Column, Spherical C18, 20 - 40 um,330; Mobile Phase A: Water (plus 10 mM NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 80 mL/min. The fractions containing desired product were collected and concentrated under reduced pressure to afford 5-fluoro-*N*-(4-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide as a yellow solid.

[00427] Yield 170 mg (40%). 1H NMR (300 MHz, Chloroform-d) δ 11.24 (s, 1H), 8.66 (d, J = 4.8 Hz, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.39 (dd, J = 8.8, 4.8 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 8.2 Hz,

1H), 7.43 -7.41 (m, 2H), 4.97 - 4.77 (m, 2H), 4.08 (t, *J* = 5.6 Hz, 2H), 3.13 – 3.11 (m, 1H), 3.01 - 2.91 (m, 1H), 2.64 (s, 3H). m/z: [ESI$^+$] 421(M+H)$^+$

Final Compounds

Synthesis of 5-(4-acetylpiperazin-1-yl)-N-(4-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide ***(Compound 117)***



Compound 117

[00428] A solution of 5-fluoro-*N*-(4-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide (50 mg, 0.119 mmol) and 1-(piperazin-1-yl)ethanone (46 mg, 0.359 mmol) in DMSO (1 mL) was stirred at 120 °C for 4 h under nitrogen atmosphere. After the reaction was completed, the mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19 x 250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 20 mL/min. The fractions containing desired product were collected and concentrated under reduced pressure to afford 5-(4-acetylpiperazin-1-yl)-*N*-(4-(2-((2-(methylsulfinyl)ethoxy)methyl)pyridin-3-yl)thiazol-2-yl)picolinamide as a white solid.

[00429] Yield 19 mg (30%). ^{1}H NMR (400 MHz, DMSO) δ 11.72 (br s, 1H), 8.56 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.42 (d, *J* = 2.8 Hz, 1H), 8.14 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.60 (s, 1H), 7.54 - 7.38 (m, 2H), 4.91 - 4.68 (m, 2H), 3.94 - 3.78 (m, 2H), 3.68 - 3.56 (m, 4H), 3.51 (t, *J* = 5.2 Hz, 2H), 3.44 (t, *J* = 5.2 Hz, 2H), 3.10 - 2.96 (m, 1H), 2.90 - 2.76 (m, 1H), 2.51 (s, 3H), 2.06 (s, 3H). m/z: [ESI+] 529 (M+H)$^+$.

EXAMPLE 2

Biological activity of compounds of the invention

[00430] The biological activity results of compounds of the invention are summarized in **Table 2**.

Table 2. Cellular EC_{50} values of compounds of the invention in the WI-38 collagen 1 inhibition assay.

Compound No.	COL1 Efficacy (LogEC_{50}) -: inactive +: > -5 ++: -5 to -6 +++: < -6 -: Inactive
100	+++
101	+++
102	+++

103	++
104	+++
105	++
106	+++
107	+++
108	+++
109	+++
110	+++
111	+++
112	+++
113	++
114	++
115	++
116	+
118	+++

EXAMPLE 3

Effect of Compound 100 on Expression of Collagen 1 in WI38 Human Lung Fibroblasts Cells (Figure 1)

[00431] WI-38 cells were plated in 384-well plate and activated with fibroblast activation cocktail for 72 hours and treated with compounds in the last 48 hours. Compound **100** was tested at the indicated concentrations (0.005, 0.014, 0.12, 0.37, 1, 3, and 10 mM). Collagen 1 levels were determined by immunofluorescence microscopy using an anti-collagen 1 antibody. Relative expression of collagen was determined and normalized to control cells treated with DMSO. Normalized collagen expression is presented on the Y-axis.

[00432] The measured EC_{50} of Compound **100** was 163 nM

EXAMPLE 4

Compound 100 Nanosuspension Preparation Protocol and Short-term Stability Analysis

[00433] Nanosuspension of Compound **100** was prepared at 100 mg/mL in a vehicle comprised of 0.5% HPMC 606, 0.5% PVP K30 and 0.1% SDS and milled for 150 minutes (at intervals of 30 min the hydrodynamic size was checked and showed no change between 90 min and 150 min).

[00434] The formulation was then placed into stability and assessed for its physical and chemical stability by HPLC assay, DLS and XRPD for up to 6 weeks.

[00435] **Figure 2** depicts the short-term stability of Nanosuspension of Compound **100** as observed by the dynamic light scattering Z-potential of size particles. The nanosuspension was prepared and stored at RT (25 °C) and at 2-8 °C and the chemical and physical stability were monitored over time.

[00436] At a define time point, the sample was vortexed for 1 minute and an aliquot was then collected, centrifuged 10 min/12500 rpm using centrifuge filter tube (nylon filter 0.45 µm) and the amount of dissolved API was quantified by HPLC. The isolated fraction was then analysed by XRPD.

[00437] Slight increase of the hydrodynamic size was observed after 7 days of storage at RT (25°C), whereas when stored at refrigerated condition the observed hydrodynamic size was comparable to t=0.

[00438] **Figure 3** depicts the short-term stability of Nanosuspension of Compound **100** as observed by HPLC assay, measuring the sample purity over time.

[00439] Nanosuspension of Compound **100** appear to be chemically and physically stable for up to 6 weeks both at RT (25 °C) and at 2-8 °C. Increase of the dissolved fraction observed from t=3 days at both storage conditions. * Standard purity at 254 nm is 99.33%

[00440] **Figures 4A-B** depict the XRPD of Nanosuspension of Compound **100** at 25^0c (**Figure 4A**) and at $2\text{-}8^0$c (**Figure 4B**). No change in the physical form of the compound was noticed after 6 weeks both at RT (25 °C) and at 2-8 °C.

EXAMPLE 5

Pharmacokinetics Data for Compound 100 (Figures 5 and 6)

[00441] Balb/C mice (fed, n=3 per group) were dosed with Compound **100** by intravenous (i.v.), 10 mg/kg) or oral administration, 3, 10 or 30 mg/kg, once in the single administration or twice-a-day (BID) with an 8-hours interval, for 1 or 5 days. Following dosing, blood samples were collected at 0.08, 0.25, 0.75, 1, 2, 3, 4, 8, 12 and 24 hours, and on day 5, at the same time points. Target compound concentration, free EC_{50} is 109 ng/ml.

[00442] **Figure 5** depicts Compound **100** single-dose, 24h IV and PO pharmacokinetic study in Balb/C mice. PK profile of Compound **100**, IV at 10mg/kg (triangles), PO at 3 (circle with solid line), 10 (circle with large hatched line) and 30mg/kg (circle with small hatch line).

[00443] IV dosing of Compound **100** shows low clearance (12% LBF, assuming mouse LBF of 120 mL/min/kg) with a half-life of 4.34 h; and moderate volume of distribution at 2.03 L/Kg.

[00444] The PK parameters for IV and PO administration in single-dose pharmacokinetics study in Balb/C mice are summarized hereinbelow in **Tables 3A-D**.

Table 3A-D. PK parameters for IV and PO administration of Compound **100** in a single-dose pharmacokinetics study in Balb/C mice.

Table 3A. IV 10 mg/kg PK Parameters for Compound **100**

IV 10 mg/kg PK Parameters	
T1/2 (h)	4.34
Cl_obs (ml/min/kg)	13.9
C0 (ng/ml)	10692
AUC last	13319
AUC inf	13445
Vss (L/kg)	2.03

Table 3B. PO 3 mg/kg PK Parameters for Compound **100**

PO 3 mg/kg PK Parameters	
T1/2 (h)	2.77
Tmax (h)	2
Cmax (ng/mL)	344
AUC last (h*ng/mL)	2465
AUC inf (h*ng/mL)	2471
MRT Inf_obs (h)	5.21
AUC last /D (h*mg/mL)	822
F (%)	61.3

Table 3C. PO 10 mg/kg PK Parameters for Compound **100**

PO 10 mg/kg PK Parameters	
T1/2 (h)	2.21
Tmax (h)	1
Cmax (ng/mL)	1250
AUC last (h*ng/mL)	8077
AUC inf (h*ng/mL)	8083
MRT Inf_obs (h)	4.78
AUC last /D (h*mg/mL)	808
F (%)	60.1

Table 3D. PO 30 mg/kg PK Parameters for Compound **100**

PO 30 mg/kg PK Parameters	
T1/2 (h)	7.24
Tmax (h)	0.75
Cmax (ng/mL)	4512
AUC last (h*ng/mL)	22442
AUC inf (h*ng/mL)	24248
MRT Inf_obs (h)	7.68
AUC last /D (h*mg/mL)	748
F (%)	60.1

[00445] Bioavailabity %F stays at same level at around 60% for all three-dosing level. No clinical sign was observed during the study.

[00446] **Figure 6** depicts a multi-dose 5-day PK Study (Day 1 and 5) of Compound **100** in Balb/C mice. PK profile: IV at 10mg/kg, PO at 3, 10, 30 and 100mg/kg (as indicated to the right of the graph). IV dosing of Compound **100** shows low clearance (11% LBF, assuming mouse LBF of 120 mL/min/kg) with a half-life of 1.9 h; and moderate volume of distribution at 1.5 L/Kg. PO Multi-dose PK study was carried out as BID for 5 days, with plasma collection on day 1 and 5 only, but administration of drug was at zero hour and eighth hour daily. Nanosuspension formulation as described above was used and prepared fresh for each day of the administration. PK parameters for IV and PO administration.

[00447] The PK parameters for IV and PO administration of Compound **100** to Balb/C mice in a multi-dose 5-day pharmacokinetics study (Day 1 and 5) are summarized hereinbelow in **Tables 4A-G**.

Table 4A-G. PK parameters for IV and PO administration of Compound **100** to Balb/C mice in a multi-dose 5-day PK Study (Day 1 and 5).

Table 4A. IV 10 mg/kg PK Parameters for Compound **100** (Day 1)

IV PK Parameters (Day 1)	
T1/2 (h)	1.9
Cl_obs (ml/min/kg)	13.2
C0 (ng/ml)	9232
AUC last	12599
AUC inf	12602
Vss (L/kg)	1.52

Table 4B. PO 3 mg/kg PK Parameters for Compound **100** (Day 1)

PO 3 mg/kg PK Parameters (Day 1)	
T1/2 (h)	2.9
Tmax (h)	0.5
Cmax (ng/mL)	1400
AUC last (h*ng/mL)	5559
AUC Inf (h*ng/mL)	3209
AUC last /D (h*mg/mL)	926
F (%)	73.5

Table 4C. PO 10 mg/kg PK Parameters for Compound **100** (Day 1)

PO 10 mg/kg PK Parameters (Day 1)	
T1/2 (h)	ND*
Tmax (h)	8.5
Cmax (ng/mL)	5153
AUC last (h*ng/mL)	22141
AUC Inf (h*ng/mL)	23133
MRT Inf_obs (h)	1107
AUC last /D (h*mg/mL)	87.9
F (%)	60.1

Table 4D. PO 30 mg/kg PK Parameters for Compound **100** (Day 1)

PO 30 mg/kg PK Parameters (Day 1)	
T1/2 (h)	ND*
Tmax (h)	8.5
Cmax (ng/mL)	8250
AUC last (h*ng/mL)	55698
AUC Inf (h*ng/mL)	ND*
AUC last /D (h*mg/mL)	928
F (%)	73.7

Table 4E. PO 3 mg/kg PK Parameters for Compound **100** (Day 5)

PO 3 mg/kg PK Parameters (Day 5)	
T1/2 (h)	ND*
Tmax (h)	0.5
Cmax (ng/mL)	1137
AUC last (h*ng/mL)	5285
AUC Inf (h*ng/mL)	5456
AUC last /D (h*mg/mL)	881

Table 4F. PO 10 mg/kg PK Parameters for Compound **100** (Day 5)

PO 10 mg/kg PK Parameters (Day 5)	
T1/2 (h)	2.5
Tmax (h)	8.5
Cmax (ng/mL)	4447
AUC last (h*ng/mL)	17988
AUC Inf (h*ng/mL)	18478
AUC last /D (h*mg/mL)	899

Table 4G. PO 30 mg/kg PK Parameters for Compound **100** (Day 5)

PO 30 mg/kg PK Parameters (Day 5)	
T1/2 (h)	3.2
Tmax (h)	8.5
Cmax (ng/mL)	7990
AUC last (h*ng/mL)	47802
AUC Inf (h*ng/mL)	ND*
AUC last /D (h*mg/mL)	797

*Rsq<0.9

Results

[00448] Bioavailabity %F stays at same level for 3mg/kg and 30mg/kg groups at 73.5 and 73.7 respectively, with a higher %F for the 10mg/kg group at 87.9 on Day 1. Slight drop off in exposure can be observed for all dosing level on Day 5, 5% for 3mg/kg group; 19% for 10mg/kg group; 15% for 30mg/kg group. No clinical sign was observed during the study.

[00449] Compound **100** shows a good plasma exposure, half life and bioavailability (**Figures 5 and 6**). A similar half-life, of ~2.5 hours, is observed between dosing regiments and doses (**Figure 5**). Target free EC_{50} value were reached for all doses in plasma up to 10 hours post dosing (**Figure 5 and 6**). IV dosing of Compound **100** shows low clearance (12% LBF, assuming mouse LBF of 120 mL/min/kg) with a half-life of 4.34 h; and moderate volume of distribution at 2.03 L/Kg. For the single-dose study, bioavailabity (%F) remained at same level at around 60% for all three-dosing level. No clinical sign was observed during the study. For the multi-dose study, bioavailabity (%F) remained at same levels for 3mg/kg and 30mg/kg groups at 73.5 and 73.7 respectively, with a higher %F for the 10mg/kg group at 87.9 on Day 1. Slight drop off in

exposure can be observed for all dosing level on Day 5, 5% for 3mg/kg group; 19% for 10mg/kg group; 15% for 30mg/kg group. No clinical sign was observed during the study.

EXAMPLE 6

Pharmacokinetics Data for Compound 100 and *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)pyridine-3-yl)thiazol-2-yl)picolinamide* (Compound A) (Figures 7 and 8)

[00450] **Figure 7** depicts the IV administration 10mg/kg single-dose PK study of Compound **100** and **Compound A**. IV administration of **Compound 100** and **Compound A** showed similar levels of exposure of the two compounds, with lower observed clearance value for **Compound 100**.

[00451] The PK parameters for IV administration of Compound **100** and **Compound A** are summarized hereinbelow in **Table 5**.

Table 5. PK parameters for IV administration of Compound **100** and **Compound A.**

IV PK parameters	Compound 100	Compound A
Cl_obs (ml/min/kg)	13.9	15.5
T1/2 (h)	4.34	2.02
C_0 (ng/ml)	10692	11115
AUC last	13319	10668
AUC inf	13445	10838
Vss (L/kg)	2.03	1.07

[00452] IV administration of Compound **100** show higher AUC last than that of Compound **A**.

[00453] **Figure 8** depicts the PO administration single-dose PK study of Compound **100** and Compound **A**. Both Compound **100** and Compound **A** were administrated as PO at 3, 10, 30mg/kg. Compound **100** showed a steady PO bioavailability at all three dosing levels. In contrast, Compound **A** showed an increased bioavailability from 32.3% to 273%, as the dosing level increased from 3 to 100 mg/kg. This phenomenon may relate to saturation of efflux transported by Compound **A** during the absorption phase.

[00454] The PK parameters for PO administration of Compound **100** and Compound **A** are summarized hereinbelow in **Tables 6A-B**.

Table 6A. Summary of Compound **100** PO plasma pharmacokinetic parameters

PK parameters	Unit	3mg/kg	10mg/kg	30mg/kg
T1/2*	h	2.77	2.21	7.24
Tmax	h	2	1	0.75
Cmax	ng/mL	344	1250	4512
AUC last	h*ng/mL	2465	8077	22442
AUC Inf	h*ng/mL	2471	8083	24248
AUC_%Extrap_obs	%	0.22	0.0688	7.45
MRTInf_obs	h	5.21	4.78	7.68
AUClast/D	h*mg/mL	822	808	748
F	%	61.3	60.1	60.1

Table 6B. Summary of Compound **A** PO plasma pharmacokinetic parameters

PK parameters	Unit	3mg/kg	10mg/kg	30mg/kg
T1/2*	h	2.99	1.92	1.65
Tmax	h	0.75	1	1
Cmax	ng/mL	394	3647	7297
AUC last	h*ng/mL	891	7100	37077
AUC Inf	h*ng/mL	1049	7333	37079
AUC_%Extrap_obs	%	15.1	3.18	0.00636
MRTInf_obs	h	3.66	2.1	4.06
AUClast/D	h*mg/mL	297	710	1236
F	%	32.3	67.7	114

[00455] **Compound 100** has higher AUC last at 3 and 10mg/kg than **Compound A**.

EXAMPLE 7

Compound 100 Efficacy in Bleomycin Induced Lung Fibrosis Mice Model – *In vivo* study (Figures 9-14)

[00456] Male C57BL/6 mice that were 7–8 weeks of age, approximately 25-28 g in weight and free of specific pathogens and had free access to food were selected to the study.

[00457] **Figure 9** depicts the study schedule.

[00458] After 1 week of adaptive feeding, the mice were weighed, their weights were recorded, and the mice were then randomly divided into two groups:

[00459] Control group (Group 1): the mice in which were given a single dose of saline intra-tracheal (n=12); and

[00460] Experimental BLM groups (n=48): the mice in which were given BLM (0.66 mg/kg, equivalent to 1U/kg) in a volume of 50 ml, intra-tracheal on day 0.

[00461] On day 7 animals were assigned based on body weight loss (%) into experimental groups (n=12 per group) and following randomization, treatment started for all groups and lasted daily until Day 21.

- Group 1 served as a negative control group and received 10 mL/kg/PO/QD of Vehicle (0.1% hydroxyethilcellulose (HEC)).
- Group 2 was a positive control and received the same Vehicle in BID regime.
- Group 5 was treated with the reference compound Nintedanib at 60 mg/kg/PO/QD.
- Groups 3 and 4 received test compound Compound **100** as follows: 10 mg/kg/BID and 30 mg/kg/BID.

[00462] On day 21, all animals were subjected to pulmonary test using whole body plethysmography (WBP).

[00463] Briefly, the machine and FinePointe software were first turned on and the device was calibrated by following instructions in the FinePointe wizard, allowing air to flow inside the chamber. Animals were gently placed inside the chamber and acclimated to the chamber. Select WBP volume and 3-minutes of

analysis data were recorded after the acclimation and box-flow (mL/min) was measured via a differential pressure sensor recording both experimental and reference chambers; lung mechanic parameters were inferred from the pressure changes produced by the animals breathing movements. At the end of the study, all mice were then sacrificed. Animal lung samples were first perfused with cold saline and 10% NBF, and then collected into tube containing 10% NBF, and processed into paraffin-embedded FFPE block.

[00464] Histopathological evaluation of lung: lung histology H&E) and specific staining of lung collagen was performed using Masson's Trichrome Staining, and fibrosis was evaluated by Modified Ashcroft scoring (**Table 7**).

Table 7. Modified Ashcroft Score

Score	Characterization Modified Ashcroft Score
0	Alveolar septa: No fibrotic burden at the most flimsy small fibers in some alveolar walls Lung structure: Normal lung
1	Alveolar septa: Isolated gentle fibrotic changes (septum≤3x thicker than normal) Lung structure: Alveoli partly enlarged and rarefied, but no fibrotic masses present
2	Alveolar septa: clearly fibrotic changes (septum >3x thicker than normal) with knot-like formation but not connected to each other Lung structure: Alveoli partly enlarged and rarefied. but no fibrotic masses
3	Alveolar septa: Contiguous fibrotic walls (septum >3x thicker than normal) predominantly in whole microscopic field Lung structure: Alveoli partly enlarged and rarefied, but no fibrotic masses
4	Alveolar septa: Variable Lung structure: single fibrotic masses (≤10% of microscopic field)
5	Alveolar septa: Variable Lung structure: Confluent fibrotic mass (>10% and≤50% of microscopic field). Lung structure severely damaged but still preserved
6	Alveolar septa: Variable, mostly not existent Lung structure: Large contiguous fibrotic masses (>50% of microscopic field). Lung architecture mostly no preserved
7	Alveolar septa: non-existent Lung structure: Alveoli nearly obliterated with fibrous masses but still up to five air bubbles
8	Alveolar septa: non-existent Lung structure: Microscopic field complete obliteration with fibrotic masses

[00465] Lung function was measured on day 6 and day 21 after Bleomycin (0.66mpk, i.t.) administration. Penh was an indicator of bronchoconstriction. Compared to the sham group, Bleomycin (0.66mpk, i.t.) administration significantly increased Penh of model animals (data not shown).

[00466] Compared to the model group, treatment with test compound Compound **100** (10mpk and 30mpk; P.O., BID), and Nintedanib (60mpk; P.O., QD) significantly decreased lung function parameter Penh at the end of the study. Test compound, Compound **100,** improved lung function in a dose-dependent manner.

[00467] By the end of the study on Day 21, a single BLM challenge has successfully induced lung fibrosis which was confirmed by increase in Ashcroft score and higher amounts of COL1A1 deposition (Masson-Trichrom staining)(**Figure 12** and **13**) as well as accumulation of lymphocytes and eosinophils in the lung of BLM/Vehicle group (H&E staining)(**Figure 10** and **11**), in comparison to Saline/Vehicle group.

[00468] Compared to the model group, treatment with test compound Compound **100** (both 10mpk and 30mpk; P.O., BID) significantly increased animal body weight at study end (data not shown); significantly decreased lung function parameter Penh (data not shown); significantly decreased Modified Ashcroft Score (**Figure 14**), lung fibrosis (**Figure 12 and 13**) and inflammation areas (**Figure 10 and 11**).

[00469] At 30 mg/kg, a significantly better dose-dependent amelioration of study endpoints was seen for Compound **100**, with respect to the one observed for Nintendanib.

EXAMPLE 8

Compound 100 Safety Panel - Binding and enzyme uptake assays

[00470] Compound **100** was tested in a safety panel in binding assay and in an enzyme uptake assay. Tested compound concentration was 10μM. Compound binding was calculated as a % inhibition of the binding of a ligand specific for each target. Compound enzyme inhibition effect was calculated as a % inhibition of control enzyme activity. The results are shown in **Table 8** below. Results showing an inhibition or stimulation higher than 50% are considered to represent significant effects of the test compounds.

Table 8. Compound **100** Safety Panel - Binding and enzyme uptake assays.

Compound 100 (10 mM)	**% Inhibition of Control Specific Binding**		
	1st	**2nd**	**Mean**
Adenosine Guinea Pig Transporter Mass Spectrometry Binding (Antagonist Ligand) Assay, Cerep	67.5	60.6	64.1
Non-Selective Rat Glycine Ion Channel Strychnine Mass Spectrometry Binding Assay, Cerep	11.3	6.5	8.9
Glutamate (Non-Selective) Rat Ion Channel Glycine (Strychnine-Insensitive),Mass Spectrometry Binding Assay, Cerep	-11	-1.4	-6.2
GABAB(B1b/B2) Human GABA B GPCR Mass Spectrometry Binding (Antagonist Ligand) Assay, Cerep	11.7	17.5	14.6
A1(h) (antagonist radioligand)	8.3	0.3	4.3
A2A(h) (agonist radioligand)	2.9	-2.6	0.2
alpha1A(h) (antagonist radioligand)	14	-5.5	4.3
alpha1B (h) (antagonist radioligand)	30.1	6.3	18.2
alpha1D(h) (antagonist radioligand)	5.8	10	7.9
alpha2A(h) (antagonist radioligand)	-5.3	-0.9	-3.1
alpha2B(h) (antagonist radioligand)	4.4	-0.6	1.9
beta1(h) (agonist radioligand)	9.4	-0.7	4.3
beta2(h) (antagonist radioligand)	-12.4	5.9	-3.3
AT1 (h) (antagonist radioligand)	7.7	-0.4	3.7
BZD (central) (agonist radioligand)	1.6	8	4.8
Cl- channel (GABA-gated) (TBOB site) (antagonist radioligand)	-31.7	-27.9	-29.8
B2 (h) (agonist radioligand)	10.8	12.3	11.5
CB1(h) (agonist radioligand)	-9.6	-28	-18.8
CB2(h) (agonist radioligand)	5.9	-12.7	-3.4
CCK1 (CCKA) (h) (agonist radioligand)	5	10.6	7.8

CCK2 (CCKB) (h) (agonist radioligand)	0.5	-0.3	0.1
D1(h) (antagonist radioligand)	12.6	4.6	8.6
D2S(h) (agonist radioligand)	1.9	-6.2	-2.2
D2L(h) (antagonist radioligand)	1.1	3	2.1
ETA(h) (agonist radioligand)	-25.6	-27.3	-26.5
GABAA1 (h) (alpha1,beta2,gamma2) (agonist radioligand)	1.1	-16	-7.5
AMPA (agonist radioligand)	-3.8	-18.8	-11.3
kainate (agonist radioligand)	0.3	-0.4	0
NMDA (antagonist radioligand)	-9.1	-10.2	-9.7
mGluR5 (h) (agonist radioligand)	-7.2	-20.7	-14
CXCR2 (IL-8B) (h) (agonist radioligand)	17.4	1.2	9.3
CCR1 (h) (agonist radioligand)	2.2	-9.3	-3.6
H1(h) (antagonist radioligand)	-3.9	1.5	-1.2
H2(h) (antagonist radioligand)	-3.8	0	-1.9
CysLT1 (LTD4)(h) (agonist radioligand)	5.4	-10.8	-2.7
MC1 (agonist radioligand)	7.8	-2.9	2.5
MC4(h) (agonist radioligand)	-2.2	-2.1	-2.2
MAO-A (antagonist radioligand)	22.5	7.6	15
M1(h) (antagonist radioligand)	15.5	11	13.3
M2 (h) (antagonist radioligand)	10.3	16.1	13.2
M3(h) (antagonist radioligand)	0.5	0.2	0.4
M4(h) (antagonist radioligand)	-20.1	-18	-19
NK1(h) (agonist radioligand)	3.3	-24.4	-10.6
Y1(h) (agonist radioligand)	1.6	3.7	2.6
N neuronal alpha4beta2 (h) (agonist radioligand)	-4.6	-2	-3.3
N muscle-type (h) (antagonist radioligand)	8	5.1	6.5
delta (DOP) (h) (agonist radioligand)	-12.7	-9.6	-11.2
kappa (h) (KOP) (agonist radioligand)	2.9	1.7	2.3
μ (MOP) (h) (agonist radioligand)	8.3	6	7.1
PPARgammah) (agonist radioligand)	-11.6	-3.6	-7.6
PAF (h) (agonist radioligand)	12.2	11.1	11.7
PCP (antagonist radioligand)	19.3	10.7	15
RARalpha (h) (agonist radioligand)	-4.7	-8.2	-6.5
5-HT1A(h) (agonist radioligand)	-11.4	10.9	-0.2
5-HT1B (h) (antagonist radioligand)	-12.5	-2.9	-7.7
5-HT2A(h) (agonist radioligand)	-2.8	0.8	-1
5-HT2B(h) (agonist radioligand)	-20.7	-16.4	-18.5
5-HT2C(h) (antagonist radioligand)	1.2	1.6	1.4
5-HT3(h) (antagonist radioligand)	-2.2	-5.5	-3.8
GR (h) (agonist radioligand)	32.3	17.8	25.1
Estrogen ER alpha (h) (agonist radioligand)	-6.6	-3.9	-5.2
PR (h) (agonist radioligand)	0	-1	-0.5
AR(h) (agonist radioligand)	7.9	3.2	5.6
V1a(h) (agonist radioligand)	-6.5	-12	-9.2
Ca2+ channel (L, dihydropyridine site) (antagonist radioligand)	8.8	-38.1	-14.7

Ca2+ channel (L, diltiazem site) (benzothiazepines) (antagonist radioligand)	45.9	18.8	32.3
Ca2+ channel (L, verapamil site) (phenylalkylamine) (antagonist radioligand)	-1.4	-4.5	-3
Ca2+ channel (N) (antagonist radioligand)	-1.5	3.1	0.8
Potassium Channel hERG (human)- [3H] Dofetilide	3.9	2	3
KV channel (antagonist radioligand)	-2	-6.8	-4.4
Na+ channel (site 2) (antagonist radioligand)	12.8	2.3	7.5
norepinephrine transporter(h) (antagonist radioligand)	-14.3	-21.4	-17.8
dopamine transporter(h) (antagonist radioligand)	-3.9	-9.3	-6.6
GABA transporter (antagonist radioligand)	0.2	0.8	0.5
5-HT transporter (h) (antagonist radioligand)	9	19.3	14.1
COX1(h)	5.5	0.7	3.1
COX2(h)	-1.7	5.4	1.8
PDE3A (h)	0.2	2.3	1.3
PDE4D2 (h)	32	34.5	33.3
ACE (h)	-7.5	-4.7	-6.1
IRK (h) (InsR)	-33.1	-25.3	-29.2
Lck kinase (h)	-14.4	-1.8	-8.1
PKCalpha (h)	2.4	3.4	2.9
acetylcholinesterase (h)	23	26.2	24.6
MAO-B (h) recombinant enzyme	6.6	8.4	7.5
ATPase (Na+/K+)	5.8	3.5	4.7

EXAMPLE 9

BBB permeability for Compounds of the invention and *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)pyridine-3-yl)thiazol-2-yl)picolinamide* (Compound A)

Table 9. Permeability Results of Test Compounds in MDCK-MDR1 Cell Line

Compound ID	$P_{app\ (A-B)}$ (10^{-6}, cm/s)*	$P_{app\ (B-A)}$ (10^{-6}, cm/s)	Efflux Ratio**	Recovery (%) AP-BL	Recovery (%) BL-AP
Metoprolol	24.71	26.63	1.08	89.63	95.31
Prazosin	13.43	26.38	1.96	77.20	84.85
Imatinib	2.76	24.10	8.72	73.24	77.01
Compound A	10.69	29.21	2.73	84.05	87.52
Compound 100	3.91	28.82	7.38	91.61	76.94
Compound 102	4.65	10.19	2.19	56.92	51.73
Compound 103	0.14	10.65	78.08	86.02	59.92
Compound 104	1.97	3.21	1.63	36.72	20.41
Compound 105	2.61	24.44	9.36	75.63	71.65
Compound 106	7.45	12.60	1.69	54.48	55.57
Compound 107	2.05	2.97	1.45	23.89	17.95
Compound 108	4.44	36.28	8.17	83.18	99.29
Compound 109	7.25	11.42	1.58	50.29	55.14

Compound 110	8.10	10.15	1.25	52.13	52.16
Compound 112	4.88	22.37	4.59	69.87	61.29
Compound 113	1.22	21.17	17.33	79.70	85.38
Compound 114	2.85	30.23	10.60	86.22	103.94
Compound 115	2.08	17.98	8.65	74.26	86.24
Compound 116	0.36	1.42	3.95	90.75	88.24
Compound 117	0.78	4.41	5.67	90.13	88.50

**Binding Criteria:*
Low permeability: Papp ≤ 1 (×10^{-6} cm/s)
Moderate permeability: 1 < Papp < 10 (×10^{-6} cm/s)
High permeability: Papp ≥ 10 (×10^{-6} cm/s)

***Substrate Potential:*
Likely: ERa ≥ 2
Poor or Non: ERa < 2
***ERa represent the efflux ratios of test compound without an inhibitor of efflux transporter(s).*

[00471] BBB permeability was evaluated using MDCK-MDR1 cells for several compounds of the invention in comparison to a reference compound, **Compound A**. The results demonstrated that all tested compounds exhibited significantly reduced P_{app} (A-B) permeability values (10^{-6} cm/s) and increased efflux ratios. Collectively, these findings indicate a notable reduction in BBB permeability and exposure for compounds of this invention relative to **Compound A**.

EXAMPLE 10

Solubility data for selected compounds of the invention

[00472] The solubility data for selected compounds of the invention with respect to progesterone and *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide* **(Compound B)** as reference compounds is presented in **Table 10** below.

Table 10. Solubility data for selected compounds of the invention with respect to progesterone and *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide* **(Compound B)** as reference compounds in PBS pH 7.4

Compound ID	Upper limit (µM)	Solubility (µM)	Comment
Progesterone	300	16.94	moderate solubility
Compound B	300	~8	low solubility
Compound 100	300	71.0	moderate solubility
Compound 102	300	46.0	moderate solubility
Compound 103	300	210.0	high solubility
Compound 105	300	25.0	moderate solubility
Compound 106	300	32.0	moderate solubility
Compound 108	300	111.0	high solubility
Compound 109	300	59.0	moderate solubility
Compound 110	300	63.0	moderate solubility
Compound 111	300	12.0	moderate solubility

Compound 112	300	11.0	moderate solubility
Compound 113	300	99.0	moderate solubility
Compound 114	300	242.0	high solubility
Compound 115	300	256.0	high solubility
Compound 116	300	267.0	high solubility
Compound 117	300	305.0	high solubility

*General guidelines used:

<10 μM – low solubility

10 μM-100 μM – moderate solubility

>100 μM – high solubility

[00473] Compounds of the invention have significantly improved solubility compared to Compound **B**, which demonstrates poor solubility (<10μM).

EXAMPLE 11

hERG channel inhibition for compounds of the invention

[00474] The potential inhibitory effect of test articles on human Ether-à-go-go related gene (hERG) channel were evaluated by using manual patch-clamp system according to the protocols as described in this report. HEK293 cell line stably transfected with hERG gene was employed in this study and Dofetilide was used as a positive control to ensure the good quality of the assay. Based on the criteria described in the report, the results are shown in Table 11 below.

Table 11. Potential inhibitory effect of selected compounds of the invention on human Ether-à-go-go related gene (hERG) channel with respect to Dofetilide and *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide* (Compound **B**) as a reference compounds.

Compound No.	hERG IC_{50} [μM]
Dofetilide[(1)]	0.016 (1)
Compound B	9.80
Compound 100	>30[(2)]
Compound 102	13.428
Compound 106	14.028
Compound 108	>30[(2)]

Low: IC_{50} > 10 μM;
Moderate: 1 μM < IC_{50} < 10 μM;
High: IC_{50} < 1 μM

(1) The IC_{50} of positive control article, Dofetilide, is in line with the literature reports and exhibits good consistency between different batches of experiment, suggesting that current study was running under appropriate conditions and results were reliable.

(2) The IC_{50} > 30 μM was reported if the fitting result of IC_{50} was greater than 30 μM or if the maximum inhibition at 30 μM was lower than 50%.

[00475] Compounds of this invention exhibit lower binding affinity to the hERG channel compared to **Compound B** (9.80 μM), suggesting a reduced risk of cardiotoxicity in vivo.

EXAMPLE 12

Comparative Data for Compound 102 and *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide* (Compound B)

[00476] **Figure 15** depicts a Cytotoxicity window of Compound **102** of this invention compared to *5-(4-acetylpiperazin-1-yl)-N-(4-(2-(methoxymethyl)phenyl)thiazol-2-yl)picolinamide* (Compound **B**) as a reference compound.

[00477] Compound **102** demonstrated a significantly improved cytotoxicity window, exceeding 100-fold compared to Compound **B**. Compound **102** exhibited enhanced efficacy (>0.5 log units) and reduced cell toxicity (<0.5 log units). In contrast, Compound **B** showed a cytotoxicity $Log_{10}(EC_{50})$ value of -5. Notably, a CTG $Log_{10}(EC_{50})$ value of -3 is considered non-toxic across all assay concentrations (EC_{50}= 1 mM), underscoring the superior safety and effectiveness of Compound **102**.

[00478] **Figures 16A-B** depict the kinetic solubility at pH 7.4 (**Figure 16A)** and hERG channel inhibition **(Figure 16B)** of Compounds **102** of this invention compared to Compound **B**.

[00479] Compound **B** has poor solubility (<10μM), while compound **102** shows significant improvement in solubility (46.33 μM) (**Figure 16A**). (*General guidelines used: <10 μM: low solubility, 10 μM-100 μM: moderate solubility, >100 μM: high solubility).

[00480] Additionally, Compound **B** has moderate hERG channel inhibition (9.80 μM), while Compound **102** displays an improvement, with lower hERG channel inhibition (13.43 μM) (**Figure 16B**). (*Potency of a test compound inhibiting hERG channel: Low: IC_{50} > 10 μM; Moderate: 1 μM < IC_{50} < 10 μM; High: IC_{50} < 1 μM.)

[00481] The data demonstrates that compared to Compound **B,** which is unsuitable for use in animal studies (PK) due to several critical issues: higher cytotoxicity (CTG), low solubility, potential cardiotoxicity (hERG), and unfavorable BBB penetration, Compound **102**, shows significantly improved profiles.

EXAMPLE 13

Experimental Methods

Cell culture

[00482] WI-38 cells (ATCC® CCL-75™) were maintained in MEM EAGLE (NEAA) W. GLUTAMIN (Biological Industries, Cat. 06-1040-15-1A) containing 10% fetal bovine serum (FBS) and 1% Penicillin-Streptomycin Solution. To synchronize the cells (cell cycle synchronization) prior to induction of collagen synthesis, the cells were starved using DMEM-low glucose supplemented without FBS for two hours and then the medium was replaced to DMEM-low glucose supplemented with 0.25% FBS for 24 hours. Following cells synchronization the cells were seeded in assay plates using DMEM-low glucose containing 10% fetal bovine serum (FBS) and 1% Penicillin-Streptomycin and 1% L-Glutamine. To induce collagen synthesis, the cells were treated with a collagen induction cocktail for the indicated time. Compounds were added with induction.

Collagen-I immunofluorescence assay

[00483] Cells in 384-well plates were fixed for 20 min in 4% paraformaldehyde (PFA, ENCO, Cat. sc-281692). Following two washes with 1xPBS, cells were treated with Triton 0.3% (Sigma, Cat T8787-250ML) for 10 minutes and then washed twice with 1xPBS. Cells were then incubated with a blocking solution, then incubated over-night at 4°C with Anti-Collagen I (Sigma-Aldrich, Cat: C 2456) antibody (and washed three times with 1xPBS. Cells were then incubated with a suitable secondary fluorescently-tagged antibody and nuclei stained with DAPI, for 1 hour, and then washed 3 times with 1xPBS.

[00484] Cell images were taken with Operetta (Perkin Elmer, USA), a wide-field fluorescence microscope at 20x magnification. After acquisition, the images were transferred to Columbus software (Perkin-Elmer) for image analysis. In Columbus, cells were identified by their nucleus, using the "Find Nuceli" module and cytoplasm was detected based on the secondary antibody channel. Subsequently, the fluorescent signal was enumerated in the identified cell region. Data was exported to a data analysis and visualization software, Tibco Spotfire, USA.

MDCK-MDR1 assay - BBB permeability

Study Design

Step 1. Preparation of MDCK-MDR1 Cells

[00485] 1) 50 µL and 25 mL of cell culture medium were added to each well of the Transwell insert and reservoir, respectively. And then the HTS transwell plates were incubated at 37 °C, 5% CO2 for 1 hour before cell seeding.

[00486] 2) MDCK-MDR1 cells were diluted to 1.56x106 cells/mL with culture medium and 50 µL of cell suspension were dispensed into the filter well of the 96-well HTS Transwell plate. Cells were cultivated for 4-8 days in a cell culture incubator at 37 °C, 5% CO_2, 95% relative humidity. Cell culture medium was replaced every other day, beginning no later than 24 hours after initial plating.

Step 2. Preparation of Stock Solutions

[00487] 10 mM stock solutions of test compounds were prepared in DMSO. The stock solutions of positive controls were prepared in DMSO at the concentration of 10 mM. Metoprolol, Prazosin and Imatinib were used as control compounds in this assay.

Step 3. Assessment of Cell Monolayer Integrity

[00488] 1) Medium was removed from the reservoir and each Transwell insert and replaced with prewarmed fresh culture medium.

[00489] 2) Transepithelial electrical resistance (TEER) across the monolayer was measured using Millicell Epithelial Volt-Ohm measuring system (Millipore, USA).

[00490] 3) The Plate was returned to the incubator once the measurement was done.

[00491] "The TEER value was calculated according to the following equation:

TEER measurement (ohms) x Area of membrane (cm^2) = TEER value (ohm•cm^2)

[00492] TEER value should be greater than 42 ohm•cm2 , which indicates the well-qualified MDCK-MDR1 monolayer."

Step 4. Assay Procedures

[00493] 1) The MDCK-MDR1 plate was removed from the incubator and washed twice with pre-warmed HBSS (10 mM HEPES, pH 7.4), and then incubated at 37 °C for 30 minutes.

[00494] 2) The stock solutions of test compounds were diluted in DMSO to get 0.2mM solutions and then diluted with HBSS (10 mM HEPES, pH 7.4) to get 1 μM working solutions. The stock solutions of controls were diluted in DMSO to get 0.2 mM solutions and then diluted with HBSS (10 mM HEPES, pH 7.4) to get 1 μM working solutions. The final concentration of DMSO in the incubation system was 0.5%.

[00495] 3) To determine the rate of drug transport in the apical to basolateral direction. 125 μL of 1 μM working solution of test compound and control compound were added to the Transwell insert (apical compartment), and transfer 50 μL sample (D_0 sample) immediately from the apical compartment to a new 96-well plate. Fill the wells in the receiver plate (basolateral compartment) with 235 μL of HBSS (10 mM HEPES, pH 7.4) .

[00496] 4) To determine the rate of drug transport in the basolateral to apical direction. 285 μL of 1 μM working solution of test compound and control compound were to the receiver plate wells (basolateral compartment), and transfer 50 μL sample (D_0 sample) immediately from the basolateral compartment to a new 96-well plate. Fill the wells in the Transwell insert (apical compartment) with 75 μL of HBSS (10 mM HEPES, pH 7.4). The assay was performed in duplicate.

[00497] 5) The plates were incubated at 37 °C for 2 hours.

[00498] 6) At the end of the incubation, 50 μL samples from donor sides (apical compartment for Ap→Bl flux, and basolateral compartment for Bl→Ap) and receiver sides (basolateral compartment for Ap→Bl flux, and apical compartment for Bl→Ap) were transferred to wells of a new 96-well plate, followed by the addition of 4 volume of cold acetonitrile containing appropriate internal standards (IS). Samples were Vortexed for 5 minutes and then centrifuged at 3,220 g for 30 minutes. An aliquot of 100 μL of the supernatant was mixed with an appropriate volume of ultra-pure water before LC-MS/MS analysis.

[00499] 7) To determine the Lucifer Yellow leakage after 2 hour transport period, stock solution of Lucifer yellow was prepared in water and diluted with HBSS (10 mM HEPES, pH 7.4) to reach the final concentration of 100 μM. 100 μL of the Lucifer yellow solution was added to each Transwell insert (apical compartment), followed by filling the wells in the receiver plate (basolateral compartment) with 300 μL of HBSS (10 mM HEPES, pH 7.4). The plates were Incubated at 37 °C for 30 mins. 80 μL samples were removed directly from the apical and basolateral wells (using the basolateral access holes) and transferred to wells of new 96 wells plates. The Lucifer Yellow fluorescence (to monitor monolayer integrity) signal was measured in a fluorescence plate reader at 485 nM excitation and 530 nM emission.

Step 5. Data Analysis

[00500] The apparent permeability coefficient (Papp), in units of centimeter per second, was calculated for MDCK-MDR1 drug transport assays using the following equation:

$$\mathbf{P_{app} = (VA \times [drug]_{acceptor}) / (Area \times Time \times [drug]_{initial,\ donor})}$$

[00501] Where VA is the volume (in mL) in the acceptor well, Area is the surface area of the membrane (0.143 cm2 for Transwell-96 Well Permeable Supports), and time is the total transport time in seconds.

[00502] The efflux ratio was determined using the following equation:

$$\mathbf{Efflux\ Ratio = P_{app}(B\text{-}A) / P_{app}(A\text{-}B)}$$

[00503] Where P_{app} (B-A) indicates the apparent permeability coefficient in basolateral to apical direction, and P_{app} (A-B) indicates the apparent permeability coefficient in apical to basolateral direction.

[00504] The recovery was determined using the following equation:

Recovery%=(VA×[drug]acceptor+VD×[drug]donor)/(VD×[drug]initial, donor)

[00505] Where VA is the volume (in mL) in the acceptor well (0.235 mL for Ap→Bl flux, and 0.075 mL for Bl→Ap), VD is the volume (in mL) in the donor well (0.075 mL for Ap→Bl flux, and 0.235 mL for Bl→Ap)

[00506] The leakage of Lucifer Yellow, in unit of percentage (%), was calculated using the following equation:

%LY leakage = 100×[LY]acceptor/([LY]donor+[LY]acceptor)

[00507] LY leakage of <1% is acceptable to indicate the well qualified MDCK-MDR1 monolayer.

MDCK-MDR1 assay bioanalytical method

1. Chromatographic conditions

[00508] LC system: Shimadzu

[00509] MS analysis: Triple QuadTM 6500+ Low Mass instrument from AB Inc (Canada) with an ESI interface

[00510] Column temperature: 40 °C

[00511] MS analysis: Triple QuadTM 5500 instrument from AB Inc (Canada) with an ESI interface

[00512] Column temperature:40 °C

[00513] Gradient and flow:

[00514] G-1.0 min-10-0.1 min, 3%B; 0.1-0.5 min, 3-100%B; 0.5-0.8 min, 100%B; 0.8-0.81 min, 100-3%B; 0.81-1.0 min, 3%B. Injection volume: 1 μL. Elution rate: 1.0 mL/min.

[00515] Column:

[00516] T3 Waters XSelect HSS T3 C18, 2.5μm, 2.1 x 50mm

Mobile phase:

[00517] MP-FAPhase A: water (0.1% formic acid); Phase B: acetonitrile (0.1% formic acid)

2. MS parameters

[00518] Ion source: Turbo spray

[00519] Ionization model: ESI

[00520] Scan type: MRM

[00521] Collision gas: 9 L/min

[00522] Curtain gas: 45 L/min

[00523] Nebulize gas: 65 L/min

[00524] Auxiliary gas: 65 L/min

[00525] Temperature: 550°C

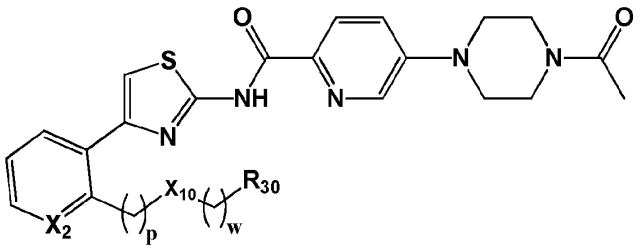
[00526] Ionspray voltage: +5500 v (positive MRM) / -4500 v (negative MRM)

CellTiter-Glo® (CTG) assay

[00527] The CellTiter-Glo® Luminescent Cell Viability Assay is a homogeneous method to determine the number of viable cells in culture based on quantifying ATP levels in cells, which signals the presence of metabolically active cells. WI-38 cells were plated in 384-well plate and activated with fibroblast activation cocktail for 72 hours and treated with compounds in the last 72 hours. CellTiter-Glo (CTG) luminescence measurement were conducted using manufacture protocol.

WHAT IS CLAIMED:

1. A compound represented by the structure of formula **IV(a)**:



IV(a)

wherein

X_2 is C or N;

X_{10} is O, NH, N(H)C(O);

w is between 0 and 3 (e.g., 0, 1, 2);

p is between 1 and 3 (e.g., 1);

R_{30} is substituted C_1-C_5 linear or branched alkyl (e.g., C(H)(OH)(CH_3)), C_2-C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C_1-C_5 linear or branched alkoxy (e.g., O-CH_3), C_1-C_5 linear or branched thioalkoxy (e.g., S-CH_3), C_1-C_5 linear, branched or cyclic haloalkyl (e.g., CHF_2), substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane), N(R_{10})(R_{11}) (e.g., N(H)(CH_3), S(O)R (e.g., S(O)-CH_3), SO_2R (e.g., SO_2-CH_3), or C(O)R;

R_{10} and **R_{11}** are each independently H, OH, substituted or unsubstituted C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched alkoxy, or substituted or unsubstituted 3-8 membered heterocyclic ring (e.g., tetrahydro-*2H*-pyrane);

or **R_{10}** and **R_{11}** are joined to form a substituted or unsubstituted 3-8 membered heterocyclic ring;

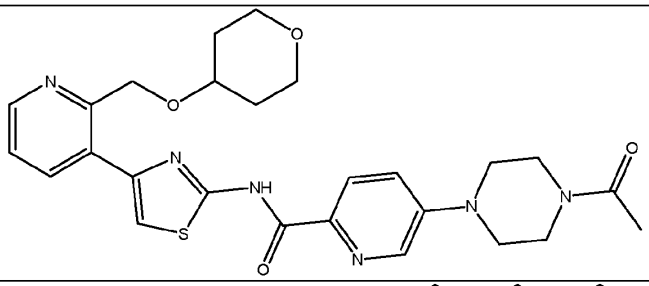
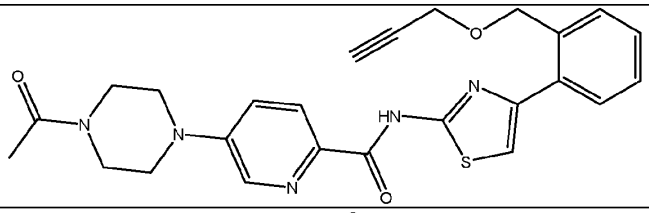
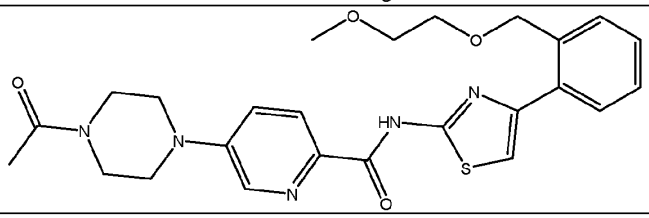
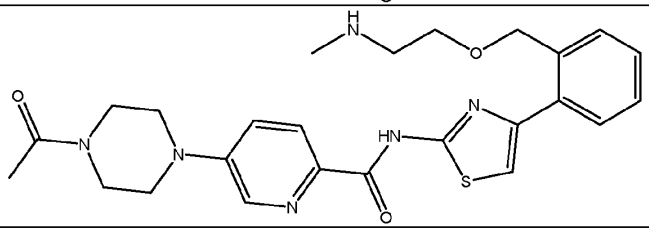
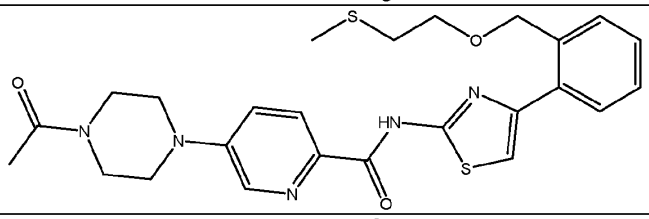
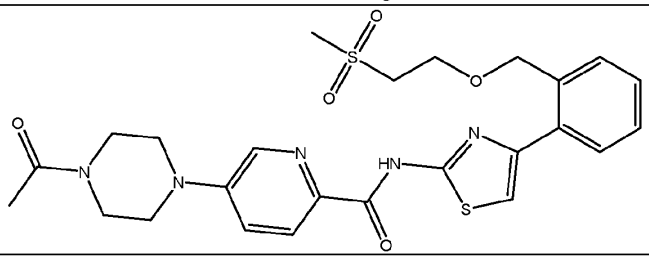
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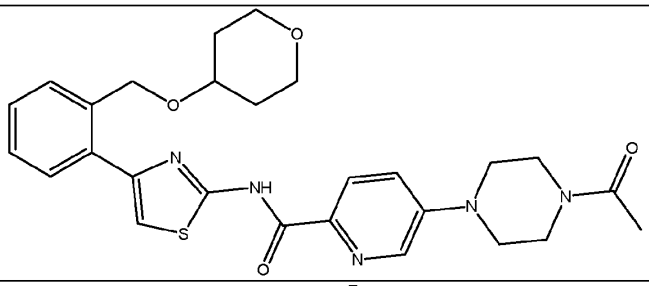
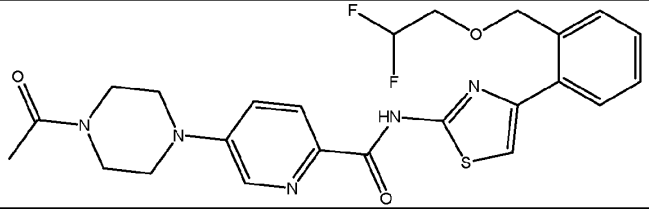
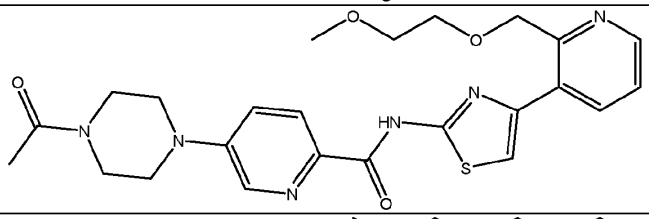
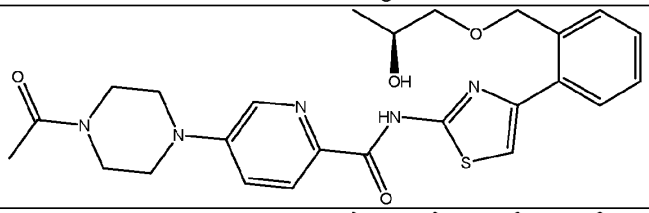
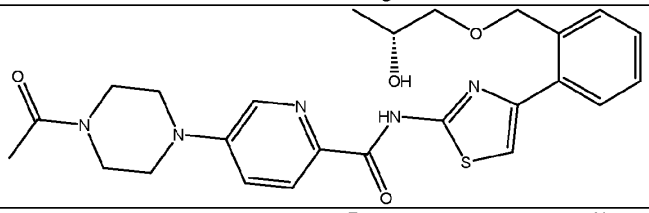
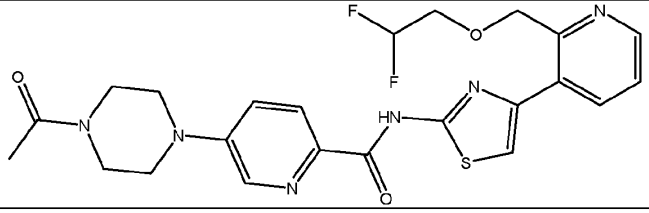
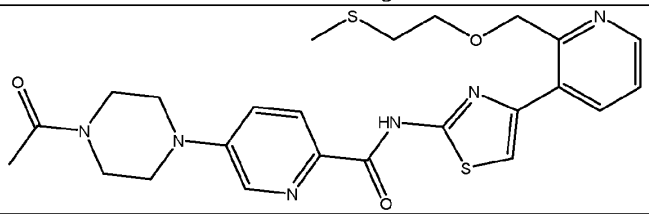
wherein the term 'substituted', as used herein for **R**, **R_{10}**, **R_{11}** and **R_{30}**, refers to substitutions selected from the group consisting of: F, Cl, Br, I, OH, CF_3, CN, NO_2, C_1-C_5 linear or branched alkoxy (e.g. OCH_3), C_2-C_5 linear or branched alkynyl (e.g. CCH), C_1-C_5 linear or branched thioalkoxy (e.g. SCH_3), C_1-C_5 linear or branched alkylsulfinyl (e.g. S(O)CH_3), C_1-C_5 linear or branched alkylsulfonyl (e.g. $S(O)_2$-CH_3), NH_2, C_1-C_5 linear or branched N(H)(alkyl) (e.g., N(H)(CH_3)) and C_1-C_5 linear or branched N(alkyl)$_2$;

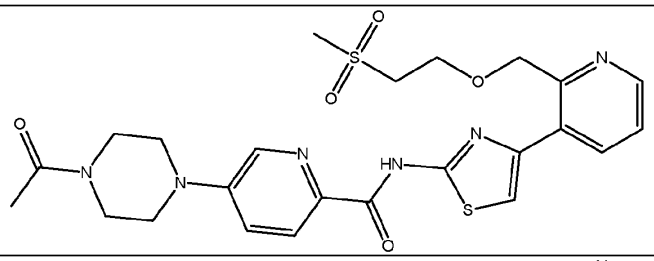
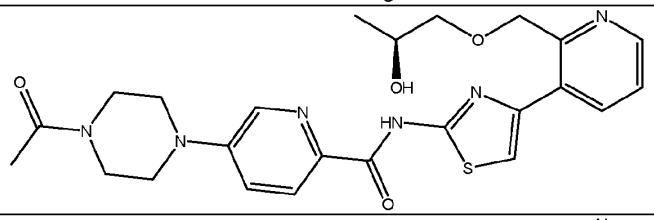
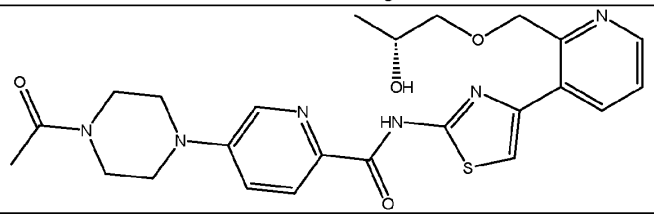
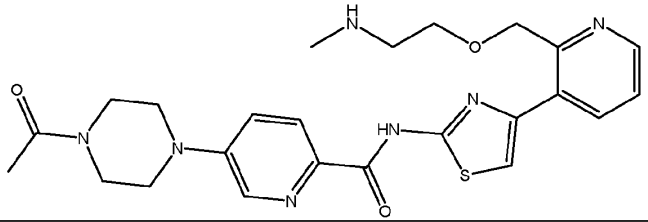
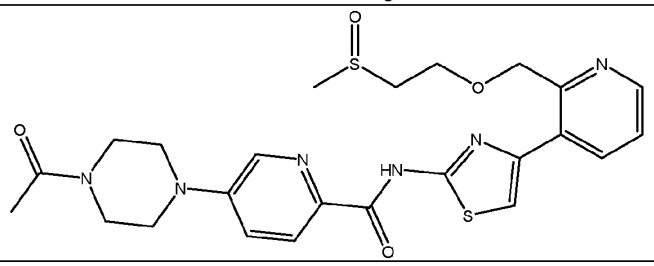
or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, isotopic variant (e.g., deuterated analog), reverse amide or any combination thereof.

2. The compound according to claim 1, represented by any one of the following structures:

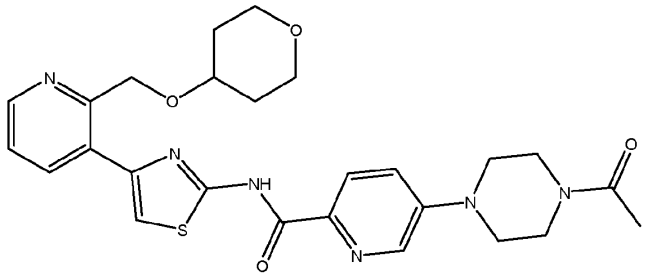
Compound Number	Compound Structure

100	
101	
102	
103	
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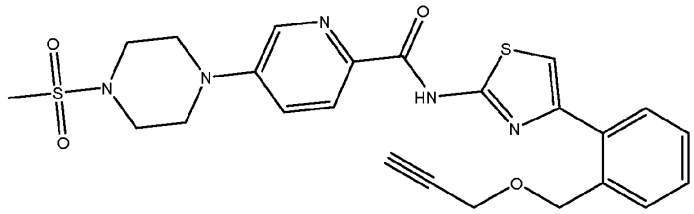
3. A compound represented by the structure of Compound **100**:



Compound **100**

or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, isotopic variant (e.g., deuterated analog), reverse amide or any combination thereof.

4. A compound represented by the structure of Compound **118**:



or its pharmaceutically acceptable salt, stereoisomer, tautomer, hydrate, *N*-oxide, isotopic variant (e.g., deuterated analog), reverse amide or any combination thereof.

5. The compound according to any one of claims 1-4, wherein the compound is a collagen translation inhibitor.

6. A pharmaceutical composition comprising a compound according to any one of claims 1-4 and a pharmaceutically acceptable carrier.

7. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting fibrosis in a subject.

8. The compound of claim 7, wherein said fibrosis is a systemic fibrotic disease.

9. The compound of claim 8, wherein said systemic fibrotic disease is systemic sclerosis, multifocal fibrosclerosis (IgG4-associated fibrosis), nephrogenic systemic fibrosis, sclerodermatous graft vs. host disease, or any combination thereof.

10. The compound of claim 7, wherein said fibrosis is an organ-specific fibrotic disease.

11. The compound of claim 10, wherein said organ-specific fibrotic disease is lung fibrosis, cardiac fibrosis, kidney fibrosis, pulmonary fibrosis, liver and portal vein fibrosis, radiation-induced fibrosis, bladder fibrosis, intestinal fibrosis, peritoneal sclerosis, diffuse fasciitis, wound healing, scaring, or any combination thereof.

12. The compound of claim 11, wherein said lung fibrosis is idiopathic pulmonary fibrosis (IPF).

13. The compound of claim 11, wherein said cardiac fibrosis is hypertension-associated cardiac fibrosis, Post-myocardial infarction, Chagas disease-induced myocardial fibrosis or any combination thereof.

14. The compound of claim 11, wherein said kidney fibrosis is diabetic and hypertensive nephropathy, urinary tract obstruction-induced kidney fibrosis, inflammatory/autoimmune-induced kidney fibrosis, aristolochic acid nephropathy, polycystic kidney disease, or any combination thereof.

15. The compound of claim 11, wherein said pulmonary fibrosis is idiopathic pulmonary fibrosis, silica-induced pneumoconiosis (silicosis), asbestos-induced pulmonary fibrosis (asbestosis), chemotherapeutic agent-induced pulmonary fibrosis, or any combination thereof.

16. The method of claim 11, wherein said liver and portal vein fibrosis is alcoholic and nonalcoholic liver fibrosis, hepatitis C-induced liver fibrosis, primary biliary cirrhosis, parasite-induced liver fibrosis (schistosomiasis), or any combination thereof.

17. The compound of claim 11, wherein said diffuse fasciitis is localized scleroderma, keloids, dupuytren's disease, peyronie's disease, myelofibrosis, oral submucous fibrosis, or any combination thereof.

18. The compound of claim 7, wherein said fibrosis is primary or secondary fibrosis.
19. The compound of claim 7 wherein said fibrosis is a result of systemic sclerosis, graft-versus host disease (GVHD), pulmonary fibrosis, autoimmune disorder, tissue injury, inflammation, oxidative stress or any combination thereof.
20. The compound of claim 7, wherein the fibrosis is hepatic fibrosis, lung fibrosis or dermal fibrosis.
21. The compound of any one of claims 7 or 16, wherein said subject has a liver cirrhosis.
22. The compound of claim 20, wherein the dermal fibrosis is scleroderma.
23. The compound of claim 20, wherein the dermal fibrosis is a result of a localized or generalized morphea, keloids, hypertrophic scars, familial cutaneous collagenoma, connective tissue nevi of the collagen type, or any combination thereof.
24. The compound of claim 20, wherein the hepatic fibrosis is a result of hepatic scarring or chronic liver injury.
25. The compound of claim 24, wherein the chronic liver injury results from alcoholism, malnutrition, hemochromatosis, exposure to poisons, toxins or drugs.
26. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting lung fibrosis in a subject.
27. The compound of claim 26, wherein the lung fibrosis is idiopathic pulmonary fibrosis (IPF).
28. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting idiopathic pulmonary fibrosis (IPF) in a subject.
29. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting hepato-fibrotic disorder in a subject.
30. The compound of claim 29, wherein the hepato-fibrotic disorder is a portal hypertension, cirrhosis, congenital hepatic fibrosis or any combination thereof.
31. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cirrhosis in a subject.
32. The compound of claim 31, wherein the cirrhosis is a result of hepatitis or alcoholism.
33. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic steatohepatitis (ASH) in a subject.
34. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non-alcoholic steatohepatitis (NASH) in a subject.
35. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting alcoholic fatty liver disease (AFLD) in a subject.

36. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting non alcoholic fatty liver disease (NAFLD) in a subject.

37. A compound according to any one of claims 1-5 or the pharmaceutical composition of claim 6, for use in treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting an autoimmune disease or disorder in a subject.