

IMIDAZOLE 3-OXIDE DERIVATIVE BASED ACSS2 INHIBITORS AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

[001] The present invention relates to novel ACSS2 inhibitors, composition and methods of preparation thereof, and uses thereof for treating viral infection (e.g. CMV), alcoholism, alcoholic steatohepatitis (ASH), non-alcoholic steatohepatitis (NASH), metabolic disorders including: obesity, weight gain and hepatic steatosis, neuropsychiatric diseases including: anxiety, depression, schizophrenia, autism and post-traumatic stress disorder, inflammatory/autoimmune conditions and cancer, including metastatic cancer, advanced cancer, and drug resistant cancer of various types.

BACKGROUND OF THE INVENTION

[002] Cancer is the second most common cause of death in the United States, exceeded only by heart disease. In the United States, cancer accounts for 1 of every 4 deaths. The 5-year relative survival rate for all cancer patients diagnosed in 1996-2003 is 66%, up from 50% in 1975-1977 (*Cancer Facts & Figures* American Cancer Society: Atlanta, GA (2008)). The rate of new cancer cases decreased by an average 0.6% per year among men between 2000 and 2009 and stayed the same for women. From 2000 through 2009, death rates from all cancers combined decreased on average 1.8% per year among men and 1.4% per year among women. This improvement in survival reflects progress in diagnosing at an earlier stage and improvements in treatment. Discovering highly effective anticancer agents with low toxicity is a primary goal of cancer research.

[003] Cell growth and proliferation are intimately coordinated with metabolism. Potentially distinct differences in metabolism between normal and cancerous cells have sparked a renewed interest in targeting metabolic enzymes as an approach to the discovery of new anticancer therapeutics.

[004] It is now appreciated that cancer cells within metabolically stressed microenvironments, herein defined as those with low oxygen and low nutrient availability (i.e., hypoxia conditions), adopt many tumour-promoting characteristics, such as genomic instability, altered cellular bioenergetics and invasive behaviour. In addition, these cancer cells are often intrinsically resistant to cell death and their physical isolation from the vasculature at the tumour site can compromise successful immune responses, drug delivery and therapeutic efficiency, thereby promoting relapse and metastasis, which ultimately translates into drastically reduced patient survival. Therefore, there is an absolute requirement to define therapeutic targets in metabolically stressed cancer cells and to develop new delivery techniques to increase therapeutic efficacy. For instance, the particular metabolic dependence of cancer cells on alternative nutrients (such as acetate) to support energy and biomass production may offer opportunities for the development of novel targeted therapies.

Acetyl-CoA synthetase enzyme, ACSS2 as a target for cancer treatment

[005] Acetyl-CoA represents a central node of carbon metabolism that plays a key role in bioenergetics, cell proliferation, and the regulation of gene expression. Highly glycolytic or hypoxic tumors must produce sufficient quantities of this metabolite to support cell growth and survival under

nutrient-limiting conditions. Acetate is an important source of acetyl-CoA in hypoxia. Inhibition of acetate metabolism may impair tumor growth. The nucleocytosolic acetyl-CoA synthetase enzyme, ACSS2, supplies a key source of acetyl-CoA for tumors by capturing acetate as a carbon source. Despite exhibiting no gross deficits in growth or development, adult mice lacking ACSS2 exhibit a significant reduction in tumor burden in two different models of hepatocellular carcinoma. ACSS2 is expressed in a large proportion of human tumors, and its activity is responsible for the majority of cellular acetate uptake into both lipids and histones. Further, ACSS2 was identified in an unbiased functional genomic screen as a critical enzyme for the growth and survival of breast and prostate cancer cells cultured in hypoxia and low serum. High expression of ACSS2 is frequently found in invasive ductal carcinomas of the breast, triple-negative breast cancer, glioblastoma, ovarian cancer, pancreatic cancer and lung cancer, and often directly correlates with higher-grade tumours and poorer survival compared with tumours that have low ACSS2 expression. These observations may qualify ACSS2 as a targetable metabolic vulnerability of a wide spectrum of tumors.

[006] Due to the nature of tumorigenesis, cancer cells constantly encounter environments in which nutrient and oxygen availability is severely compromised. In order to survive these harsh conditions, cancer cell transformation is often coupled with large changes in metabolism to satisfy the demands for energy and biomass imposed by continued cellular proliferation. Several recent reports discovered that acetate is used as an important nutritional source by some types of breast, prostate, liver and brain tumors in an acetyl-CoA synthetase 2 (ACSS2)-dependent manner. It was shown that acetate and ACSS2 supplied a significant fraction of the carbon within the fatty acid and phospholipid pools (Comerford *et al.* Cell **2014**; Mashimo *et al.* Cell **2014**; Schug *et al.* Cancer Cell **2015***). High levels of ACSS2 due to copy-number gain or high expression were found to correlate with disease progression in human breast prostate and brain tumors. Furthermore, ACSS2, which is essential for tumor growth under hypoxic conditions, is dispensable for the normal growth of cells, and mice lacking ACSS2 demonstrated normal phenotype (Comerford *et al.* **2014**). The switch to increased reliance on ACSS2 is not due to genetic alterations, but rather due to metabolic stress conditions in the tumor microenvironment. Under normal oxidative conditions, acetyl-CoA is typically produced from citrate via citrate lyase activity. However, under hypoxia, when cells adapt to anaerobic metabolism, acetate becomes a key source for acetyl-CoA and hence, ACSS2 becomes essential and is, *de facto*, synthetically lethal with hypoxic conditions (see Schug *et al.*, *Cancer Cell*, **2015**, 27:1, pp. 57-71). The accumulative evidence from several studies suggests that ACSS2 may be a targetable metabolic vulnerability of a wide spectrum of tumors.

[007] In certain tumors expressing ACSS2, there is a strict dependency on acetate for their growth or survival, then selective inhibitors of this nonessential enzyme might represent an unusually ripe opportunity for the development of new anticancer therapeutics. If the normal human cells and tissues are not heavily reliant on the activity of the ACSS2 enzyme, it is possible that such agents might inhibit the growth of ACSS2-expressing tumors with a favorable therapeutic window.

[008] 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 $\leq$ 20-30 g/day. On the contrary, AFLD is defined as the presence of steatosis and alcohol consumption >20 -30 g/day.

[009] Hepatocyte ethanol metabolism produces free acetate as its endproduct which, largely in other tissues, can be incorporated into acetyl-coenzyme A (acetylcoA) for use in Krebs cycle oxidation, fatty acid synthesis, or as a substrate for protein acetylation. This conversion is catalyzed by the acyl-coenzyme A synthetase short-chain family members 1 and 2 (ACSS1 and ACSS2). The role of acetyl-coA synthesis in control of inflammation opens a novel field of study into the relationship between cellular energy supply and inflammatory disease. It has been shown that ethanol enhances macrophage cytokine production by uncoupling gene transcription from its normal regulatory mechanisms through increased histone acetylation, and that the conversion of the ethanol metabolite acetate to acetyl-coA is crucial to this process.

[0010] It was suggested that inflammation is enhanced in acute alcoholic hepatitis in which acetyl-coA synthetases are up-regulated and convert the ethanol metabolite acetate to an excess of acetyl-coA which increases proinflammatory cytokine gene histone acetylation by increased substrate concentration and histone deacetylases (HDAC) inhibition, leading to enhanced gene expression and perpetuation of the inflammatory response. The clinical implication of these findings is that modulation of HDAC or ACSS activity might affect the clinical course of alcoholic liver injury in humans. If inhibitors of ACSS1 and 2 can modulate ethanol- associated histone changes without affecting the flow of acetyl-coA through the normal metabolic pathways, then they have the potential to become much needed effective therapeutic options in acute alcoholic hepatitis. Therefore, synthesis of metabolically available acetyl-coA from acetate is critical to the increased acetylation of proinflammatory gene histones and consequent enhancement of the inflammatory response in ethanol-exposed macrophages. This mechanism is a potential therapeutic target in acute alcoholic hepatitis.

[0011] Cytosolic acetyl-CoA is the precursor of multiple anabolic reactions including de-novo fatty acids (FA) synthesis. Inhibition of FA synthesis may favorably affect the morbidity and mortality associated with Fatty-liver metabolic syndromes (Wakil SJ, Abu-Elheiga LA. 2009. 'Fatty acid metabolism: Target for metabolic syndrome'. *J. Lipid Res.*) and because of the pivotal role of Acetyl-CoA Carboxylase (ACC) in regulating fatty acid metabolism, ACC inhibitors are under investigation as clinical drug targets in several metabolic diseases, including nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Inhibition of ACSS2 is expected to directly reduce fatty-acid accumulation in the liver through its effect on Acetyl-CoA flux from acetate that is present in the liver at high levels due to the hepatocyte ethanol metabolism. Furthermore, ACSS2 inhibitors are expected to have a better safety profile than ACC inhibitors since they are expected only to affect the flux from Acetate that is not a major source for Ac-CoA in normal conditions (Harriman G *et. al.*, 2016. "Acetyl-CoA carboxylase inhibition by ND-630 reduces hepatic steatosis, improves insulin sensitivity, and

modulates dyslipidemia in rats" *PNAS*). In addition, mice lacking ACSS2 showed reduced body weight and hepatic steatosis in a diet-induced obesity model (Z. Huang et al., ACSS2 promotes systemic fat storage and utilization through selective regulation of genes involved in lipid metabolism *PNAS* 115, (40), E9499-E9506, 2018).

5 [0012] ACSS2 is also shown to enter the nucleus under certain condition (hypoxia, high fat etc.) and to affect histone acetylation and crotonylation by making available acetyl-CoA and crotonyl-CoA and thereby regulate gene expression. For example, ACSS2 decrease is shown to lower levels of nuclear acetyl-CoA and histone acetylation in neurons affecting the the expression of many neuronal genes. In the hippocampus such reductions in ACSS2 lead to effects on memory and neuronal plasticity (Mews
10 P, et al., *Nature*, Vol 546, 381, 2017). Such epigenetic modifications are implicated in neuropsychiatric diseases such as anxiety, PTSD, depression etc. (Graff, J et al. Histone acetylation: molecular mnemonics on chromatin. *Nat Rev. Neurosci.* 14, 97-111 (2013)). Thus, an inhibitor of ACSS2 may find useful application in these conditions.

[0013] Nuclear ACSS2 is also shown to promote lysosomal biogenesis, autophagy and to promote brain
15 tumorigenesis by affecting Histone H3 acetylation (Li, X et al.: Nucleus-Translocated ACSS2 Promotes Gene Transcription for Lysosomal Biogenesis and Autophagy, *Molecular Cell* 66, 1-14, 2017). In addition, nuclear ACSS2 is shown to activate HIF-2alpha by acetylation and thus accelerate growth and metastasis of HIF2alpha-driven cancers such as certain Renal Cell Carcinoma and Glioblastomas (Chen,
R. et al. Coordinate regulation of stress signaling and epigenetic events by ACSS2 and HIF-2 in cancer
20 cells, *Plos One*, 12 (12) 1-31, 2017).

SUMMARY OF THE INVENTION

[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 formula
25 **I-IX**, and by the structures listed in Table 1, as defined herein below. In various embodiments, the compound is an Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2) inhibitor.

[0015] This invention further provides a pharmaceutical composition comprising 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
30 combination thereof, represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, and a pharmaceutically acceptable carrier.

[0016] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer comprising administering a compound represented by the structure of formula **I- IX**, and by the structures listed in Table 1, as defined herein below, to a
35 subject suffering from cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit said cancer. In various embodiments, the cancer is selected from the list of: hepatocellular carcinoma, melanoma (e.g., BRAF mutant melanoma), glioblastoma, breast cancer (e.g., invasive ductal carcinomas of the breast, triple-negative breast cancer), prostate cancer, liver

cancer, brain cancer, ovarian cancer, lung cancer, Lewis lung carcinoma (LLC), colon carcinoma, pancreatic cancer, renal cell carcinoma and mammary carcinoma. In various embodiments, the cancer is early cancer, advanced cancer, invasive cancer, metastatic cancer, drug resistant cancer or any combination thereof. In various embodiments, the subject has been previously treated with chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof. In various embodiments, the compound is administered in combination with an anti-cancer therapy. In various embodiments, the anti-cancer therapy is chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, or any combination thereof.

[0017] This invention further provides a method of suppressing, reducing or inhibiting tumour growth in a subject, comprising administering a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from cancer under conditions effective to suppress, reduce or inhibit said tumour growth in said subject. In various embodiments, the tumor growth is enhanced by increased acetate uptake by cancer cells of said cancer. In various embodiments, the increased acetate uptake is mediated by ACSS2. In various embodiments, the cancer cells are under hypoxic stress. In various embodiments, the tumor growth is suppressed due to suppression of lipid (e.g., fatty acid) synthesis and/or histones synthesis induced by ACSS2 mediated acetate metabolism to acetyl-CoA. In various embodiments, the tumor growth is suppressed due to suppressed regulation of histones acetylation and function induced by ACSS2 mediated acetate metabolism to acetyl-CoA.

[0018] This invention further provides a method of suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function in a cell, comprising contacting a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, with a cell under conditions effective to suppress, reduce or inhibit lipid synthesis and/or regulating histones acetylation and function in said cell. In various embodiments, the cell is a cancer cell.

[0019] This invention further provides a method of binding an ACSS2 inhibitor compound to an ACSS2 enzyme, comprising the step of contacting an ACSS2 enzyme with an ACSS2 inhibitor compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme.

[0020] This invention further provides a method of suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell, comprising contacting a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, with a cell, under conditions effective to suppress, reduce or inhibit acetyl-CoA synthesis from acetate in said cell. In various embodiments, the cell is a cancer cell. In various embodiments, the synthesis is mediated by ACSS2.

[0021] This invention further provides a method of suppressing, reducing or inhibiting acetate metabolism in a cancer cell, comprising contacting a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, with a cancer cell, under conditions

effective to suppress, reduce or inhibit acetate metabolism in said cells. In various embodiments, the acetate metabolism is mediated by ACSS2. In various embodiments, the cancer cell is under hypoxic stress.

[0022] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting human alcoholism in a subject, comprising administering a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, 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.

[0023] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a viral infection in a subject, comprising administering a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from a viral infection under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the viral infection in said subject. In various embodiments, the viral infection is human cytomegalovirus (HCMV) infection.

[0024] 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-IX**, 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.

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

[0026] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a metabolic disorder in a subject, comprising administering a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from metabolic disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit metabolic disorder in said subject. In various embodiment, the metabolic disorder is selected from: obesity, weight gain, hepatic steatosis and fatty liver disease.

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

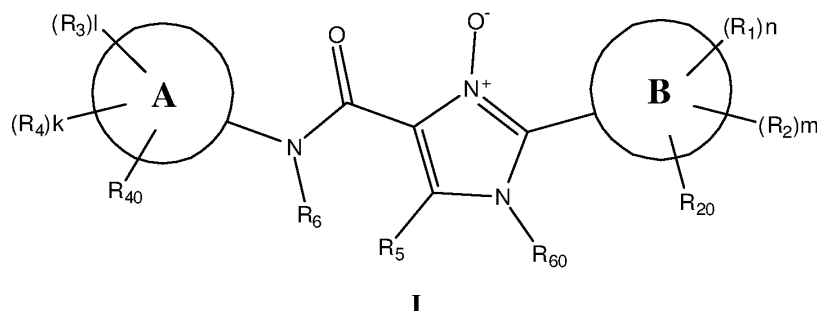
developing, or inhibit neuropsychiatric disease or disorder in said subject. In some embodiments, the neuropsychiatric disease or disorder is selected from: anxiety, depression, schizophrenia, autism and post-traumatic stress disorder.

[0028] This invention further provides a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting inflammatory condition in a subject, comprising administering a compound represented by the structure of formula **I-IX**, and by the structures listed in Table 1, as defined herein below, to a subject suffering from inflammatory condition under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit inflammatory condition in said subject.

[0029] 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-IX**, 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.

DETAILED DESCRIPTION OF THE INVENTION

[0030] In various embodiments, this invention is directed to a compound represented by the structure of formula **I**:



wherein

A and **B** rings are each independently a single or fused aromatic or heteroaromatic ring system (e.g., phenyl, indole, benzofuran, 2-, 3- or 4-pyridine, naphthalene, thiazole, thiophene, imidazole, 1-methylimidazole, benzimidazole,), or a single or fused C₃-C₁₀ cycloalkyl (e.g. cyclohexyl) or a single or fused C₃-C₁₀ heterocyclic ring (e.g., benzofuran-2(3H)-one, benzo[d][1,3]dioxole, tetrahydrothiophene 1,1-dioxide, piperidine, 1-methylpiperidine, isoquinoline, and 1,3-dihydroisobenzofuran);

R₁, **R₂** and **R₂₀** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂,

CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluorophenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), CH(CF₃)(NH-R₁₀);

or **R₂** and **R₁** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

R₃, **R₄** and **R₄₀** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., CH₂-O-CH₃) CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, R₈-N(R₁₀)(R₁₁) (e.g., CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂, C(O)N(CH₃)(CH₂CH₃), C(O)N(CH₃)(CH₂CH₂-O-CH₃), C(S)N(R₁₀)(R₁₁) (e.g., C(S)NH(CH₃)), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂NH(CH₃), SO₂N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH₃)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CF₂-cyclobutyl, CF₂-cyclopropyl, CF₂-methylcyclopropyl, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃,

CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂, C(OH)₂CF₃, cyclopropyl-CF₃), C₁-C₅ linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., CF₃-cyclopropyl, cyclopropyl, cyclopentyl), substituted or
 5 unsubstituted C₃-C₈ heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), CH(CF₃)(NH-R₁₀);

or **R₃** and **R₄** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic
 10 or aromatic, carbocyclic or heterocyclic ring (e.g., imidazole, [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);

R₅ is H, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH₂SH, ethyl, iso-propyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl, C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C₁-C₅ linear or branched haloalkyl (e.g., CF₃, CF₂CH₃,
 15 CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), **R₈**-aryl (e.g., CH₂-Ph), C(=CH₂)-R₁₀ (e.g., C(=CH₂)-C(O)-OCH₃, C(=CH₂)-CN) substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R₆ is H, C₁-C₅ linear or branched alkyl (e.g., methyl), C(O)R, or S(O)₂R;

R₆₀ is H, substituted or unsubstituted C₁-C₅ linear or branched alkyl (e.g., methyl, CH₂-
 20 OC(O)CH₃, CH₂-PO₄H₂, CH₂-PO₄H-tBu, CH₂-OP(O)(OCH₃)₂), C(O)R, or S(O)₂R;

R₈ is [CH₂]_p

wherein **p** is between 1 and 10;

R₉ is [CH]_q, [C]_q

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

R₁₀ and **R₁₁** are each independently H, CN, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl),
 25 **R₈**-O-R₁₀ (e.g., CH₂CH₂-O-CH₃), C(O)R (e.g., C(O)(OCH₃)), or S(O)₂R;

or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

R is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy
 30 (e.g., methoxy), phenyl, aryl or heteroaryl,

or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

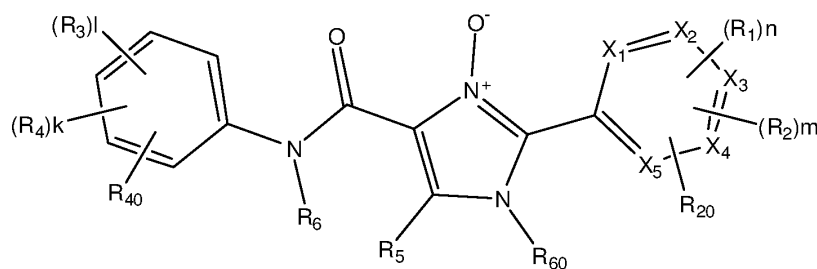
m, **n**, **l** and **k** are each independently an integer between 0 and 4 (e.g., 0, 1 or 2);

wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or
 35 branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, **R₈**-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring

(e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

[0031] In various embodiments, this invention is directed to a compound represented by the structure of formula II:



II

wherein

R₁, **R₂** and **R₂₀** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated

or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluorophenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), $\text{CH}(\text{CF}_3)(\text{NH-R}_{10})$;

or **R₂** and **R₁** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

R₃, **R₄** and **R₄₀** are each independently H, F, Cl, Br, I, OH, SH, $\text{R}_8\text{-OH}$ (e.g., $\text{CH}_2\text{-OH}$), $\text{R}_8\text{-SH}$, $\text{-R}_8\text{-O-R}_{10}$, (e.g., $\text{CH}_2\text{-O-CH}_3$) CF_3 , CD_3 , OCD_3 , CN, NO_2 , $\text{-CH}_2\text{CN}$, $\text{-R}_8\text{CN}$, NH_2 , NHR , N(R)_2 , $\text{R}_8\text{-N(R}_{10})(\text{R}_{11})$ (e.g., $\text{CH}_2\text{-NH}_2$, $\text{CH}_2\text{-N(CH}_3)_2$) $\text{R}_9\text{-R}_8\text{-N(R}_{10})(\text{R}_{11})$, B(OH)_2 , -OC(O)CF_3 , $\text{-OCH}_2\text{Ph}$, -NHCO-R_{10} (e.g., NHC(O)CH_3), $\text{NHCO-N(R}_{10})(\text{R}_{11})$ (e.g., $\text{NHC(O)N(CH}_3)_2$), COOH , -C(O)Ph , C(O)O-R_{10} (e.g., C(O)O-CH_3 , $\text{C(O)O-CH}_2\text{CH}_3$), $\text{R}_8\text{-C(O)-R}_{10}$ (e.g., $\text{CH}_2\text{C(O)CH}_3$), C(O)H , C(O)-R_{10} (e.g., C(O)-CH_3 , $\text{C(O)-CH}_2\text{CH}_3$, $\text{C(O)-CH}_2\text{CH}_2\text{CH}_3$), $\text{C}_1\text{-C}_5$ linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -C(O)NH_2 , C(O)NHR (e.g., $\text{C(O)NH(CH}_3)_2$), $\text{C(O)N(R}_{10})(\text{R}_{11})$ (e.g., $\text{C(O)N(CH}_3)_2$, $\text{C(O)N(CH}_3)(\text{CH}_2\text{CH}_3)$, $\text{C(O)N(CH}_3)(\text{CH}_2\text{CH}_2\text{-O-CH}_3)$, $\text{C(S)N(R}_{10})(\text{R}_{11})$ (e.g., $\text{C(S)NH(CH}_3)_2$), C(O)-pyrrolidine , C(O)-azetidine , $\text{C(O)-methylpiperazine}$, C(O)-piperidine , C(O)-morpholine , SO_2R , $\text{SO}_2\text{N(R}_{10})(\text{R}_{11})$ (e.g., $\text{SO}_2\text{NH(CH}_3)_2$, $\text{SO}_2\text{N(CH}_3)_2$), $\text{C}_1\text{-C}_5$ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $\text{C(OH)(CH}_3)(\text{Ph})$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted $\text{C}_1\text{-C}_5$ linear or branched or $\text{C}_3\text{-C}_8$ cyclic haloalkyl (e.g., CF_3 , CF_2CH_3 , $\text{CF}_2\text{-cyclobutyl}$, $\text{CF}_2\text{-cyclopropyl}$, $\text{CF}_2\text{-methylcyclopropyl}$, CH_2CF_3 , $\text{CF}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CF}_3$, $\text{CF}_2\text{CH(CH}_3)_2$, $\text{CF(CH}_3)_2$, C(OH)CF_3 , cyclopropyl- CF_3), $\text{C}_1\text{-C}_5$ linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, $\text{O-CH}_2\text{-cyclopropyl}$), $\text{C}_1\text{-C}_5$ linear or branched thioalkoxy, $\text{C}_1\text{-C}_5$ linear or branched haloalkoxy, $\text{C}_1\text{-C}_5$ linear or branched alkoxyalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_8$ cycloalkyl (e.g., $\text{CF}_3\text{-cyclopropyl}$, cyclopropyl, cyclopentyl), substituted or unsubstituted $\text{C}_3\text{-C}_8$ heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $\text{CH}(\text{CF}_3)(\text{NH-R}_{10})$;

or **R₃** and **R₄** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., imidazole, [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);

R₅ is H, $\text{C}_1\text{-C}_5$ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH_2SH , ethyl, iso-propyl), $\text{C}_2\text{-C}_5$ linear or branched, substituted or unsubstituted alkenyl, $\text{C}_2\text{-C}_5$ linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), $\text{C}_1\text{-C}_5$ linear or branched haloalkyl (e.g., CF_3 , CF_2CH_3 , CH_2CF_3 , $\text{CF}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CF}_3$, $\text{CF}_2\text{CH(CH}_3)_2$, $\text{CF(CH}_3)_2$), $\text{R}_8\text{-aryl}$ (e.g., $\text{CH}_2\text{-Ph}$), $\text{C(=CH}_2\text{)-R}_{10}$ (e.g., $\text{C(=CH}_2\text{)-C(O)-OCH}_3$, $\text{C(=CH}_2\text{)-CN}$) substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine);

R₆ is H, $\text{C}_1\text{-C}_5$ linear or branched alkyl (e.g., methyl), C(O)R , or $\text{S(O)}_2\text{R}$;

R₆₀ is H, substituted or unsubstituted C₁-C₅ linear or branched alkyl (e.g., methyl, CH₂-OC(O)CH₃, CH₂-PO₄H₂, CH₂-PO₄H-tBu, CH₂-OP(O)(OCH₃)₂), C(O)R, or S(O)₂R;

R₈ is [CH₂]_p

wherein **p** is between 1 and 10;

5 **R₉** is [CH]_q, [C]_q

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

R₁₀ and **R₁₁** are each independently H, CN, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), R₈-O-R₁₀ (e.g., CH₂CH₂-O-CH₃), C(O)R (e.g., C(O)(OCH₃)), or S(O)₂R;

10 or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

R is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

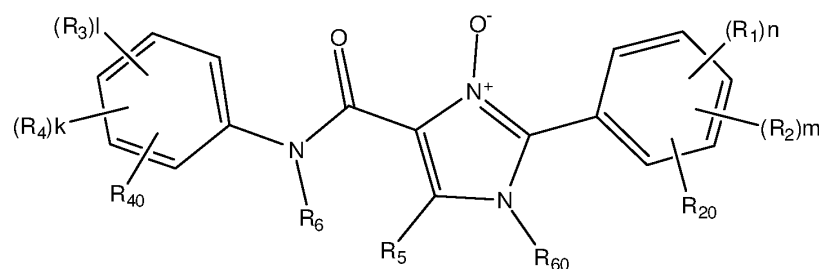
X₁, **X₂**, **X₃**, **X₄** and **X₅** are each independently C or N;

15 **m**, **n**, **l** and **k** are each independently an integer between 0 and 4 (e.g., 0, 1 or 2);

wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

[0032] In various embodiments, this invention is directed to a compound represented by the structure of formula **III**:



III

30 wherein

R₁, **R₂** and **R₂₀** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN,

NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluorophenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), CH(CF₃)(NH-R₁₀);

or **R₂** and **R₁** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

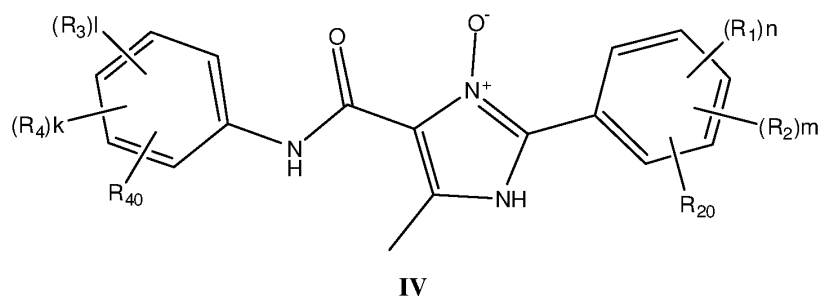
R₃, **R₄** and **R₄₀** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., CH₂-O-CH₃) CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, R₈-N(R₁₀)(R₁₁) (e.g., CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂, C(O)N(CH₃)(CH₂CH₃), C(O)N(CH₃)(CH₂CH₂-O-CH₃), C(S)N(R₁₀)(R₁₁) (e.g., C(S)NH(CH₃)), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂NH(CH₃), SO₂N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH₃)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CF₂-

- cyclobutyl, CF₂-cyclopropyl, CF₂-methylecyclopropyl, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂, C(OH)₂CF₃, cyclopropyl-CF₃, C₁-C₅ linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., CF₃-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), CH(CF₃)(NH-R₁₀);
- or **R₃** and **R₄** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., imidazole, [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);
- R₅** is H, C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, CH₂SH, ethyl, iso-propyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl, C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CCH), C₁-C₅ linear or branched haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), R₈-aryl (e.g., CH₂-Ph), C(=CH₂)-R₁₀ (e.g., C(=CH₂)-C(O)-OCH₃, C(=CH₂)-CN) substituted or unsubstituted aryl (e.g., phenyl), substituted or unsubstituted heteroaryl (e.g., pyridine (2, 3, and 4-pyridine));
- R₆** is H, C₁-C₅ linear or branched alkyl (e.g., methyl), C(O)R, or S(O)₂R;
- R₆₀** is H, substituted or unsubstituted C₁-C₅ linear or branched alkyl (e.g., methyl, CH₂-OC(O)CH₃, CH₂-PO₄H₂, CH₂-PO₄H-tBu, CH₂-OP(O)(OCH₃)₂), C(O)R, or S(O)₂R;
- R₈** is [CH₂]_p
wherein **p** is between 1 and 10;
- R₉** is [CH]_q, [C]_q
wherein **q** is between 2 and 10;
- R₁₀** and **R₁₁** are each independently H, CN, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), R₈-O-R₁₀ (e.g., CH₂CH₂-O-CH₃), C(O)R (e.g., C(O)(OCH₃)), or S(O)₂R;
- or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),
- R** is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;
- m**, **n**, **l** and **k** are each independently an integer between 0 and 4 (e.g., 0, 1 or 2);
wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring

(e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

[0033] In various embodiments, this invention is directed to a compound represented by the structure of formula IV:



wherein

R₁, **R₂** and **R₂₀** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated

or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluorophenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), $\text{CH}(\text{CF}_3)(\text{NH-R}_{10})$;

or R_2 and R_1 are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

R_3 , R_4 and R_{40} are each independently H, F, Cl, Br, I, OH, SH, $\text{R}_8\text{-OH}$ (e.g., $\text{CH}_2\text{-OH}$), $\text{R}_8\text{-SH}$, $\text{-R}_8\text{-O-R}_{10}$, (e.g., $\text{CH}_2\text{-O-CH}_3$) CF_3 , CD_3 , OCD_3 , CN, NO_2 , $\text{-CH}_2\text{CN}$, $\text{-R}_8\text{CN}$, NH_2 , NHR , N(R)_2 , $\text{R}_8\text{-N(R}_{10})(\text{R}_{11})$ (e.g., $\text{CH}_2\text{-NH}_2$, $\text{CH}_2\text{-N(CH}_3)_2$) $\text{R}_9\text{-R}_8\text{-N(R}_{10})(\text{R}_{11})$, B(OH)_2 , -OC(O)CF_3 , $\text{-OCH}_2\text{Ph}$, -NHCO-R_{10} (e.g., NHC(O)CH_3), $\text{NHCO-N(R}_{10})(\text{R}_{11})$ (e.g., $\text{NHC(O)N(CH}_3)_2$), COOH , -C(O)Ph , C(O)O-R_{10} (e.g., C(O)O-CH_3 , $\text{C(O)O-CH}_2\text{CH}_3$), $\text{R}_8\text{-C(O)-R}_{10}$ (e.g., $\text{CH}_2\text{C(O)CH}_3$), C(O)H , C(O)-R_{10} (e.g., C(O)-CH_3 , $\text{C(O)-CH}_2\text{CH}_3$, $\text{C(O)-CH}_2\text{CH}_2\text{CH}_3$), $\text{C}_1\text{-C}_5$ linear or branched C(O)-haloalkyl (e.g., C(O)-CF_3), -C(O)NH_2 , C(O)NHR (e.g., $\text{C(O)NH(CH}_3)$), $\text{C(O)N(R}_{10})(\text{R}_{11})$ (e.g., $\text{C(O)N(CH}_3)_2$, $\text{C(O)N(CH}_3)(\text{CH}_2\text{CH}_3)$, $\text{C(O)N(CH}_3)(\text{CH}_2\text{CH}_2\text{-O-CH}_3)$, $\text{C(S)N(R}_{10})(\text{R}_{11})$ (e.g., $\text{C(S)NH(CH}_3)$), C(O)-pyrrolidine , C(O)-azetidine , $\text{C(O)-methylpiperazine}$, C(O)-piperidine , C(O)-morpholine , SO_2R , $\text{SO}_2\text{N(R}_{10})(\text{R}_{11})$ (e.g., $\text{SO}_2\text{NH(CH}_3)$, $\text{SO}_2\text{N(CH}_3)_2$), $\text{C}_1\text{-C}_5$ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, $\text{C(OH)(CH}_3)(\text{Ph})$, ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted $\text{C}_1\text{-C}_5$ linear or branched or $\text{C}_3\text{-C}_8$ cyclic haloalkyl (e.g., CF_3 , CF_2CH_3 , $\text{CF}_2\text{-cyclobutyl}$, $\text{CF}_2\text{-cyclopropyl}$, $\text{CF}_2\text{-methylcyclopropyl}$, CH_2CF_3 , $\text{CF}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CF}_3$, $\text{CF}_2\text{CH(CH}_3)_2$, $\text{CF(CH}_3)_2$, C(OH)_2CF_3 , cyclopropyl- CF_3), $\text{C}_1\text{-C}_5$ linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, $\text{O-CH}_2\text{-cyclopropyl}$), $\text{C}_1\text{-C}_5$ linear or branched thioalkoxy, $\text{C}_1\text{-C}_5$ linear or branched haloalkoxy, $\text{C}_1\text{-C}_5$ linear or branched alkoxyalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_8$ cycloalkyl (e.g., $\text{CF}_3\text{-cyclopropyl}$, cyclopropyl, cyclopentyl), substituted or unsubstituted $\text{C}_3\text{-C}_8$ heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), $\text{CH}(\text{CF}_3)(\text{NH-R}_{10})$;

or R_3 and R_4 are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., imidazole, [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);

R_8 is $[\text{CH}_2]_p$

wherein p is between 1 and 10;

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

wherein q is between 2 and 10;

R_{10} and R_{11} are each independently H, CN, $\text{C}_1\text{-C}_5$ linear or branched alkyl (e.g., methyl, ethyl), $\text{R}_8\text{-O-R}_{10}$ (e.g., $\text{CH}_2\text{CH}_2\text{-O-CH}_3$), C(O)R (e.g., $\text{C(O)(OCH}_3)$), or $\text{S(O)}_2\text{R}$;

or R_{10} and R_{11} are joined to form a substituted or unsubstituted $\text{C}_3\text{-C}_8$ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

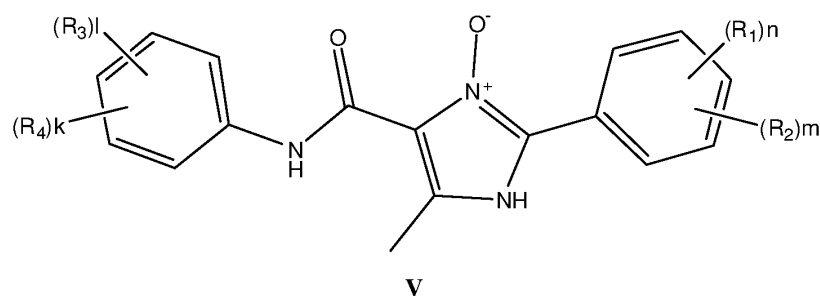
R is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

m, **n**, **l** and **k** are each independently an integer between 0 and 4 (e.g., 0, 1 or 2);

- 5 wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring
- 10 (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

- 15 [0034] In various embodiments, this invention is directed to a compound represented by the structure of formula **V**:



wherein

- 20 **R₁** and **R₂** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g.,
- 25 NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g. C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g.,
- 30 C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈

cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluoroxyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), CH(CF₃)(NH-R₁₀);

or **R₂** and **R₁** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

R₃ and **R₄** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., CH₂-O-CH₃) CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, R₈-N(R₁₀)(R₁₁) (e.g., CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂, C(O)N(CH₃)(CH₂CH₃), C(O)N(CH₃)(CH₂CH₂-O-CH₃), C(S)N(R₁₀)(R₁₁) (e.g., C(S)NH(CH₃)), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂NH(CH₃), SO₂N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH₃)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CF₂-cyclobutyl, CF₂-cyclopropyl, CF₂-methylecyclopropyl, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂, C(OH)₂CF₃, cyclopropyl-CF₃), C₁-C₅ linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., CF₃-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., oxadiazole, pyrrol, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), CH(CF₃)(NH-R₁₀);

or **R₃** and **R₄** are joint together to form a 5 or 6 membered or **R₃** and **R₄** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., imidazole, [1,3]dioxole, furan-2(3H)-one, benzene, cyclopentane, imidazole);

R₈ is [CH₂]_p

5 wherein **p** is between 1 and 10;

R₉ is [CH]_q, [C]_q

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

R₁₀ and **R₁₁** are each independently H, CN, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), R₈-O-R₁₀ (e.g., CH₂CH₂-O-CH₃), C(O)R (e.g., C(O)(OCH₃)), or S(O)₂R;

10 or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

R is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

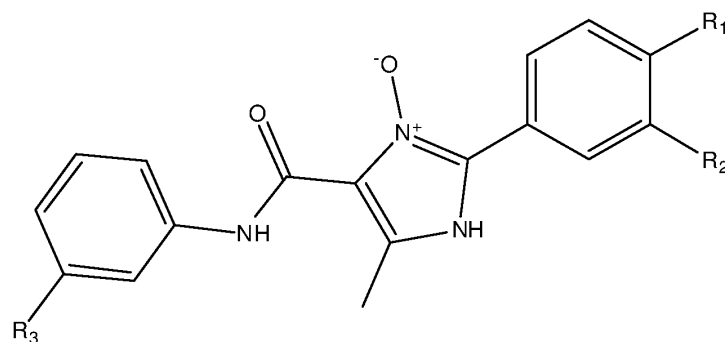
15 **m**, **n**, **l** and **k** are each independently an integer between 0 and 4 (e.g., 0, 1 or 2);

wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

25

[0035] In various embodiments, this invention is directed to a compound represented by the structure of formula **VI**:



VI

30 wherein

R₁ and **R₂** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluorophenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), CH(CF₃)(NH-R₁₀);

or **R₂** and **R₁** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

R₃ is H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., CH₂-O-CH₃) CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, R₈-N(R₁₀)(R₁₁) (e.g., CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂, C(O)N(CH₃)(CH₂CH₃), C(O)N(CH₃)(CH₂CH₂-O-CH₃), C(S)N(R₁₀)(R₁₁) (e.g., C(S)NH(CH₃)), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂NH(CH₃),

SO₂N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH₃)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CF₂-cyclobutyl, CF₂-cyclopropyl, CF₂-methylcyclopropyl, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂, C(OH)₂CF₃, cyclopropyl-CF₃), C₁-C₅ linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., CF₃-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., oxadiazole, pyrrol, *N*-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), CH(CF₃)(NH-R₁₀);

R₈ is [CH₂]_p

wherein **p** is between 1 and 10;

R₉ is [CH]_q, [C]_q

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

R₁₀ and **R₁₁** are each independently H, CN, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), R₈-O-R₁₀ (e.g., CH₂CH₂-O-CH₃), C(O)R (e.g., C(O)(OCH₃)), or S(O)₂R;

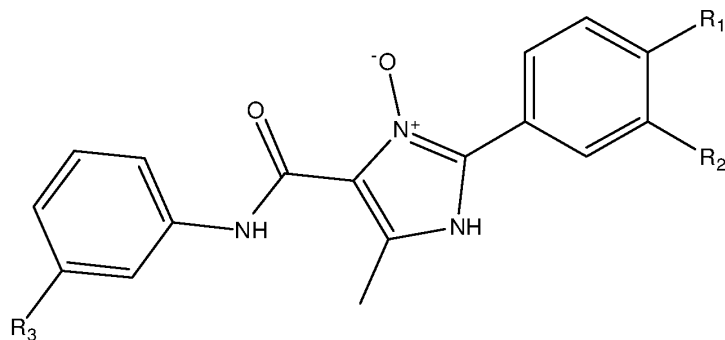
or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

R is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

[0036] In various embodiments, this invention is directed to a compound represented by the structure of formula **VII**:



VII

wherein

- 5 **R₁** and **R₂** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluorophenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), CH(CF₃)(NH-R₁₀);

or **R₂** and **R₁** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

R₃ is C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂, C(O)N(CH₃)(CH₂CH₃), C(O)N(CH₃)(CH₂CH₂-O-CH₃), C(S)N(R₁₀)(R₁₁) (e.g., C(S)NH(CH₃)), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO₂N(R₁₀)(R₁₁) (e.g., SO₂NH(CH₃), SO₂N(CH₃)₂), or substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CF₂-cyclobutyl, CF₂-cyclopropyl, CF₂-methylcyclopropyl, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂, C(OH)₂CF₃, cyclopropyl-CF₃), CH(CF₃)(NH-R₁₀);

R₈ is [CH₂]_p

wherein **p** is between 1 and 10;

R₉ is [CH]_q, [C]_q

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

R₁₀ and **R₁₁** are each independently H, CN, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), R₈-O-R₁₀ (e.g., CH₂CH₂-O-CH₃), C(O)R (e.g., C(O)(OCH₃)), or S(O)₂R;

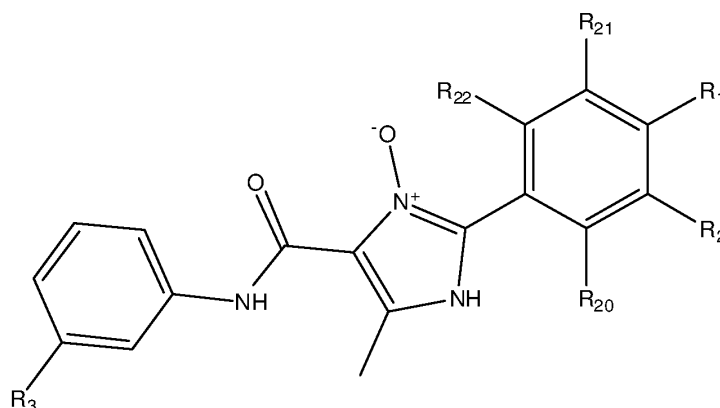
or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

R is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

[0037] In various embodiments, this invention is directed to a compound represented by the structure of formula **VIII**:



VIII

- R₁, R₂, R₂₀, R₂₁ and R₂₂** are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluorophenyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), CH(CF₃)(NH-R₁₀);

or **R₂** and **R₁** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

5 or **R₂₁** and **R₁** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

or **R₂₁** and **R₂₂** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

10 **R₃** is H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., CH₂-O-CH₃) CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, R₈-N(R₁₀)(R₁₁) (e.g., CH₂-NH₂, CH₂-N(CH₃)₂) R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g. C(O)O-CH₃, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂, C(O)N(CH₃)(CH₂CH₃), C(O)N(CH₃)(CH₂CH₂-O-CH₃), C(S)N(R₁₀)(R₁₁) (e.g., C(S)NH(CH₃)), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂NH(CH₃), SO₂N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl, C(OH)(CH₃)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CF₂-cyclobutyl, CF₂-cyclopropyl, CF₂-methylcyclopropyl, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂, C(OH)₂CF₃, cyclopropyl-CF₃), C₁-C₅ linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., CF₃-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., oxadiazole, pyrrol, N-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), (wherein substitutions include: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy, N(R)₂, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO₂ or any combination thereof), CH(CF₃)(NH-R₁₀);

R₈ is [CH₂]_p

wherein **p** is between 1 and 10;

R₉ is [CH]_q, [C]_q

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

R₁₀ and **R₁₁** are each independently H, CN, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), R₈-O-R₁₀ (e.g., CH₂CH₂-O-CH₃), C(O)R (e.g., C(O)(OCH₃)), or S(O)₂R;

or **R**₁₀ and **R**₁₁ are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

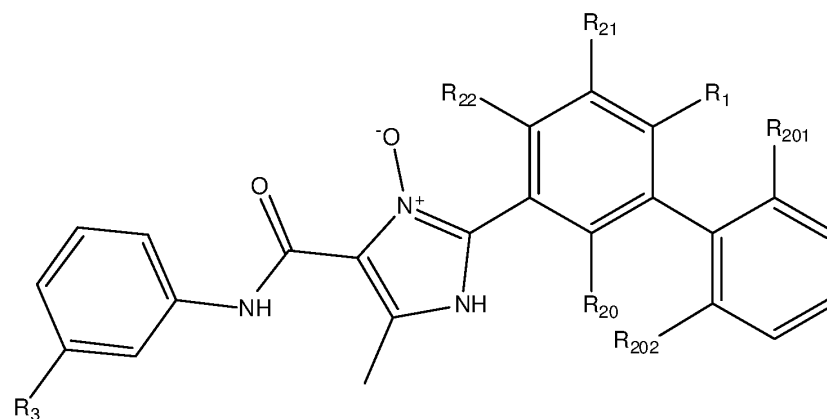
R is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem **R** substituents are joint together to form a 5 or 6
5 membered heterocyclic ring;

wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g.,
10 CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

[0038] In some embodiments, **R**₁ is methoxy. In some embodiments, **R**₂ is xylyl. In some embodiments, **R**₃ is haloalkyl. In some embodiments, **R**₃ is CF₃, CF₂CH₃, CF₂-cyclopropyl, CH₂CF₃, CF₂CH₂CH₃, C(OH)₂CF₃ or cyclopropyl-CF₃; each represents a separate embodiment according to this invention. In some embodiments, **R**₁ is methoxy, **R**₂ is xylyl and **R**₃ is haloalkyl.

20 [0039] In various embodiments, this invention is directed to a compound represented by the structure of formula **IX**:



IX

R₁, **R**₂₀, **R**₂₁ and **R**₂₂ are each independently H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., -CH₂-O-CH₃), R₈-(C₃-C₈ cycloalkyl) (e.g., cyclohexyl), R₈-(C₃-C₈ heterocyclic ring) (e.g., CH₂-morpholine, CH₂-imidazole, CH₂-indazole), CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR (e.g., NH-CH₃), N(R)₂ (e.g., N(CH₃)₂), R₈-N(R₁₀)(R₁₁) (e.g., CH₂-CH₂-N(CH₃)₂, CH₂-NH₂, CH₂-N(CH₃)₂), R₉-R₈-N(R₁₀)(R₁₁) (e.g., C≡C-CH₂-NH₂), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, NHC(O)-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph,

C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH(CH₃)₂, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR, C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂), SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂N(CH₃)₂, SO₂NHC(O)CH₃), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., C(H)(OH)-CH₃, methyl, 2, 3, or 4-CH₂-C₆H₄-Cl, ethyl, propyl, iso-propyl, butyl, t-Bu, iso-butyl, pentyl, benzyl), C₂-C₅ linear or branched, substituted or unsubstituted alkenyl (e.g., CH=C(Ph)₂), C₁-C₅ linear, branched or cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy (e.g. methoxy, O-(CH₂)₂-pyrrolidine, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl, O-cyclobutyl, O-cyclopentyl, O-cyclohexyl, 1-butoxy, 2-butoxy, O-tBu), optionally wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (e.g., O-1-oxacyclobutyl, O-2-oxacyclobutyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy (e.g., OCF₃, OCHF₂), C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., morpholine, piperidine, piperazine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, oxadiazole, imidazole, furane, triazole, tetrazole, pyridine (2, 3, or 4-pyridine), 3-methyl-2-pyridine, pyrimidine, pyrazine, pyridazine, oxacyclobutane (1 or 2-oxacyclobutane), indole, protonated or deprotonated pyridine oxide), substituted or unsubstituted aryl (e.g., phenyl, xylyl, 2,6-difluorophenyl, 4-fluoroxilyl), substituted or unsubstituted benzyl (e.g., benzyl, 4-Cl-benzyl, 4-OH-benzyl), CH(CF₃)(NH-R₁₀);

or **R**₂₁ and **R**₁ are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

or **R**₂₁ and **R**₂₂ are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring (e.g., pyrrol, [1,3]dioxole, furan-2(3H)-one, benzene, pyridine);

R₂₀₁ and **R**₂₀₂ are each independently H, F, Cl, Br, I, CF₃, or C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl);

R₃ is H, F, Cl, Br, I, OH, SH, R₈-OH (e.g., CH₂-OH), R₈-SH, -R₈-O-R₁₀, (e.g., CH₂-O-CH₃) CF₃, CD₃, OCD₃, CN, NO₂, -CH₂CN, -R₈CN, NH₂, NHR, N(R)₂, R₈-N(R₁₀)(R₁₁) (e.g., CH₂-NH₂, CH₂-N(CH₃)₂) R₉-R₈-N(R₁₀)(R₁₁), B(OH)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-R₁₀ (e.g., NHC(O)CH₃), NHCO-N(R₁₀)(R₁₁) (e.g., NHC(O)N(CH₃)₂), COOH, -C(O)Ph, C(O)O-R₁₀ (e.g., C(O)O-CH₃, C(O)O-CH₂CH₃), R₈-C(O)-R₁₀ (e.g., CH₂C(O)CH₃), C(O)H, C(O)-R₁₀ (e.g., C(O)-CH₃, C(O)-CH₂CH₃, C(O)-CH₂CH₂CH₃), C₁-C₅ linear or branched C(O)-haloalkyl (e.g., C(O)-CF₃), -C(O)NH₂, C(O)NHR (e.g., C(O)NH(CH₃)), C(O)N(R₁₀)(R₁₁) (e.g., C(O)N(CH₃)₂, C(O)N(CH₃)(CH₂CH₃), C(O)N(CH₃)(CH₂CH₂-O-CH₃), C(S)N(R₁₀)(R₁₁) (e.g., C(S)NH(CH₃)), C(O)-pyrrolidine, C(O)-azetidine, C(O)-methylpiperazine, C(O)-piperidine, C(O)-morpholine, SO₂R, SO₂N(R₁₀)(R₁₁) (e.g., SO₂NH(CH₃), SO₂N(CH₃)₂), C₁-C₅ linear or branched, substituted or unsubstituted alkyl (e.g., methyl,

C(OH)(CH₃)(Ph), ethyl, propyl, iso-propyl, t-Bu, iso-butyl, pentyl), substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl (e.g., CF₃, CF₂CH₃, CF₂-cyclobutyl, CF₂-cyclopropyl, CF₂-methylcyclopropyl, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂, CF(CH₃)-CH(CH₃)₂, C(OH)₂CF₃, cyclopropyl-CF₃), C₁-C₅ linear, branched or cyclic alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, O-CH₂-cyclopropyl), C₁-C₅ linear or branched thioalkoxy, C₁-C₅ linear or branched haloalkoxy, C₁-C₅ linear or branched alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., CF₃-cyclopropyl, cyclopropyl, cyclopentyl), substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., oxadiazole, pyrrol, N-methyloxetane-3-amine, 3-methyl-4H-1,2,4-triazole, 5-methyl-1,2,4-oxadiazole, thiophene, oxazole, isoxazole, imidazole, furane, triazole, methyl-triazole, pyridine (2, 3, or 4-pyridine), pyrimidine, pyrazine, oxacyclobutane (1 or 2-oxacyclobutane), indole), substituted or unsubstituted aryl (e.g., phenyl), (wherein substitutions include: F, Cl, Br, I, C₁-C₅ linear or branched alkyl, OH, alkoxy, N(R)₂, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO₂ or any combination thereof), CH(CF₃)(NH-R₁₀);

R₈ is [CH₂]_p

wherein **p** is between 1 and 10;

R₉ is [CH]_q, [C]_q

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

R₁₀ and **R₁₁** are each independently H, CN, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), R₈-O-R₁₀ (e.g., CH₂CH₂-O-CH₃), C(O)R (e.g., C(O)(OCH₃)), or S(O)₂R;

or **R₁₀** and **R₁₁** are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring (e.g., pyrrolidine, piperazine, methylpiperazine, azetidine, piperidine, morpholine),

R is H, C₁-C₅ linear or branched alkyl (e.g., methyl, ethyl), C₁-C₅ linear or branched alkoxy (e.g., methoxy), phenyl, aryl or heteroaryl, or two gem R substituents are joint together to form a 5 or 6 membered heterocyclic ring;

wherein substitutions include: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂;

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

[0040] 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, 5 benzo[c]thiophenyl, benzodioxolyl, benzo[d][1,3]dioxole, thiadiazolyl, [1,3]oxazolo[4,5-b]pyridine, oxadiazolyl, 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-10 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, each definition is a separate embodiment according to this invention; or **A** is C₃-C₈ cycloalkyl (e.g. cyclohexyl) or C₃-C₈ heterocyclic 15 ring including but not limited to: tetrahydropyran, piperidine, 1-methylpiperidine, tetrahydrothiophene 1,1-dioxide, 1-(piperidin-1-yl)ethanone or morpholine.

[0041] 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-20 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, 25 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, oxadiazolyl, 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, C₃-C₈ cycloalkyl, 30 or C₃-C₈ heterocyclic ring including but not limited to: tetrahydropyran, piperidine, 1-methylpiperidine, tetrahydrothiophene 1,1-dioxide, 1-(piperidin-1-yl)ethanone or morpholine; each definition is a separate embodiment according to this invention.

- [0042] In some embodiments, the **A** ring 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 4-pyridinyl. In other embodiments, **A** is naphthyl. In other embodiments, **A** is benzothiazolyl. In other embodiments, **A** is benzimidazolyl. In other embodiments, **A** is quinolinyl. In other embodiments, **A** is isoquinolinyl. In other embodiments, **A** is indolyl. In other embodiments, **A** is tetrahydronaphthyl. In other embodiments, **A** is indenyl. In other embodiments, **A** is benzofuran-2(3H)-one. In other embodiments, **A** is benzo[d][1,3]dioxole. In other embodiments, **A** is naphthalene. In other embodiments, **A** is tetrahydrothiophene1,1-dioxide. In other embodiments, **A** is thiazole. In other embodiments, **A** is benzimidazole. In others embodiment, **A** is piperidine. In other embodiments, **A** is 1-methylpiperidine. In other embodiments, **A** is imidazole. In other embodiments, **A** is 1-methylimidazole. In other embodiments, **A** is thiophene. In other embodiments, **A** is isoquinoline. In other embodiments, **A** is indole. In other embodiments, **A** is 1,3-dihydroisobenzofuran. In other embodiments, **A** is benzofuran. In other embodiments, **A** is single or fused C₃-C₁₀ cycloalkyl ring. In other embodiments, **A** is cyclohexyl.
- [0043] 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. In other embodiments, **B** is naphthyl. In other embodiments, **B** is indolyl. In other embodiments, **B** is benzimidazolyl. In other embodiments, **B** is benzothiazolyl. In other embodiments, **B** is quinoxalinyl. In other embodiments, **B** is tetrahydronaphthyl. In other embodiments, **B** is quinolinyl. In other embodiments, **B** is isoquinolinyl. In other embodiments, **B** is indenyl. In other embodiments, **B** is naphthalene. In other embodiments, **B** is tetrahydrothiophene1,1-dioxide. In other embodiments, **B** is thiazole. In other embodiments, **B** is benzimidazole. In other embodiments, **B** is piperidine. In other embodiments, **B** is 1-methylpiperidine. In other embodiments, **B** is imidazole. In other embodiments, **B** is 1-methylimidazole. In other embodiments, **B** is thiophene. In other embodiments, **B** is isoquinoline. In other embodiments, **B** is indole. In other embodiments, **B** is 1,3-dihydroisobenzofuran. In other embodiments, **B** is benzofuran. In other embodiments, **B** is single or fused C₃-C₁₀ cycloalkyl ring. In other embodiments, **B** is cyclohexyl.
- [0044] In some embodiments, **X₁** of compound of formula **II** is C. In other embodiments, **X₁** is N.
- [0045] In some embodiments, **X₂** of compound of formula **II** is C. In other embodiments, **X₂** is N.
- [0046] In some embodiments, **X₃** of compound of formula **II** is C. In other embodiments, **X₃** is N.
- [0047] In some embodiments, **X₄** of compound of formula **II** is C. In other embodiments, **X₄** is N.
- [0048] In some embodiments, **X₅** of compound of formula **II** is C. In other embodiments, **X₅** is N.

[0049] In various embodiments, compound of formula **I-IV** is substituted by R₁, R₂ and R₂₀ and compound of formula **V** is substituted by R₁ and R₂. Single substituents can be present at the *ortho*, *meta*, or *para* positions.

[0050] In various embodiments, compound of formula **I-V** is substituted by R₃ and R₄. Single substituents can be present at the *ortho*, *meta*, or *para* positions. In various embodiments, compound of formula **I-IV** is substituted by R₄₀. Single substituents can be present at the *ortho*, *meta*, or *para* positions.

[0051] In some embodiments, **R₁** of formula **I-IX** is H. In some embodiments, **R₁** is not H.

[0052] In other embodiments, **R₁** of formula **I-IX** is F. In other embodiments, R₁ is Cl. In other embodiments, R₁ is Br. In other embodiments, R₁ is I. In other embodiments, R₁ is OH. In other embodiments, R₁ is R₈-(C₃-C₈ cycloalkyl). In other embodiments, R₁ is CH₂-cyclohexyl. In other embodiments, R₁ is R₈-(C₃-C₈ heterocyclic ring). In other embodiments, R₁ is CH₂-morpholine. In other embodiments, R₁ is CH₂-imidazole. In other embodiments, R₁ is CH₂-indazole. In other embodiments, R₁ is CF₃. In other embodiments, R₁ is CN. In other embodiments, R₁ is CF₂CH₂CH₃. In other embodiments, R₁ is CH₂CH₂CF₃. In other embodiments, R₁ is CF₂CH(CH₃)₂. In other embodiments, R₁ is CF(CH₃)-CH(CH₃)₂. In other embodiments, R₁ is OCD₃. In other embodiments, R₁ is NO₂. In other embodiments, R₁ is NH₂. In other embodiments, R₁ is NHR. In other embodiments, R₁ is NH-CH₃. In other embodiments, R₁ is N(R)₂. In other embodiments, R₁ is N(CH₃)₂. In other embodiments, R₁ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₁ is CH₂-CH₂-N(CH₃)₂. In other embodiments, R₁ is CH₂-NH₂. In other embodiments, R₁ is CH₂-N(CH₃)₂. In other embodiments, R₁ is R₉-R₈-N(R₁₀)(R₁₁). In other embodiments, R₁ is C≡C-CH₂-NH₂. In other embodiments, R₁ is B(OH)₂. In other embodiments, R₁ is NHC(O)-R₁₀. In other embodiments, R₁ is NHC(O)CH₃. In other embodiments, R₁ is NHCO-N(R₁₀)(R₁₁). In other embodiments, R₁ is NHC(O)N(CH₃)₂. In other embodiments, R₁ is COOH. In other embodiments, R₁ is C(O)-R₁₀. In other embodiments, R₁ is C(O)-CH₃. In other embodiments, R₁ is C(O)O-R₁₀. In other embodiments, R₁ is C(O)O-CH(CH₃)₂. In other embodiments, R₁ is C(O)O-CH₃. In other embodiments, R₁ is SO₂N(R₁₀)(R₁₁). In other embodiments, R₁ is SO₂N(CH₃)₂. In other embodiments, R₁ is SO₂NHC(O)CH₃. In other embodiments, R₁ is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other embodiments, R₁ is methyl. In other embodiments, R₁ is ethyl. In other embodiments, R₁ is iso-propyl. In other embodiments, R₁ is Bu. In other embodiments, R₁ is t-Bu. In other embodiments, R₁ is iso-butyl. In other embodiments, R₁ is pentyl. In other embodiments, R₁ is propyl. In other embodiments, R₁ is benzyl. In other embodiments, R₁ is C(H)(OH)-CH₃. In other embodiments, R₁ is C₂-C₅ linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R₁ is CH=C(Ph)₂. In other embodiments, R₁ is 2-CH₂-C₆H₄-Cl. In other embodiments, R₁ is 3-CH₂-C₆H₄-Cl. In other embodiments, R₁ is 4-CH₂-C₆H₄-Cl. In other embodiments, R₁ is ethyl. In other embodiments, R₁ is iso-propyl. In other embodiments, R₁ is t-Bu. In other embodiments, R₁ is iso-butyl. In other embodiments, R₁ is pentyl. In other embodiments, R₁ is substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl). In other embodiments, R₁ is substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₁ is substituted C₁-C₅ linear or

branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₁ is O-(CH₂)₂-pyrrolidine. In other
embodiments, R₁ is unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other
embodiments, R₁ is methoxy. In other embodiments, R₁ is ethoxy. In other embodiments, R₁ is propoxy.
In other embodiments, R₁ is isopropoxy. In other embodiments, R₁ is O-CH₂-cyclopropyl. In other
5 embodiments, R₁ is O-cyclobutyl. In other embodiments, R₁ is O-cyclopentyl. In other embodiments,
R₁ is O-cyclohexyl. In other embodiments, R₁ is O-1-oxacyclobutyl. In other embodiments, R₁ is O-2-
oxacyclobutyl. In other embodiments, R₁ is 1-butoxy. In other embodiments, R₁ is 2-butoxy. In other
embodiments, R₁ is O-tBu. In other embodiments, R₁ is C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy
wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (O). In other
10 embodiments, R₁ is O-1-oxacyclobutyl. In other embodiments, R₁ is O-2-oxacyclobutyl. In other
embodiments, R₁ is C₁-C₅ linear or branched haloalkoxy. In other embodiments, R₁ is OCF₃. In other
embodiments, R₁ is OCHF₂. In other embodiments, R₁ is substituted or unsubstituted C₃-C₈ cycloalkyl.
In other embodiments, R₁ is cyclopropyl. In other embodiments, R₁ is cyclopentyl. In other
embodiments, R₁ is cyclohexyl. In other embodiments, R₁ is substituted or unsubstituted C₃-C₈
15 heterocyclic ring. In other embodiments, R₁ is morpholine. In other embodiments, R₁ is piperidine. In
other embodiments, R₁ is piperazine. In other embodiments, R₁ is oxazole. In other embodiments, R₁ is
methyl substituted oxazole. In other embodiments, R₁ is oxadiazole. In other embodiments, R₁ is methyl
substituted oxadiazole. In other embodiments, R₁ is imidazole. In other embodiments, R₁ is methyl
substituted imidazole. In other embodiments, R₁ is pyridine. In other embodiments, R₁ is 2-pyridine. In
20 other embodiments, R₁ is 3-pyridine. In other embodiments, R₁ is 3-methyl-2-pyridine. In other
embodiments, R₁ is 4-pyridine. In other embodiments, R₁ is tetrazole. In other embodiments, R₁ is
pyrimidine. In other embodiments, R₁ is pyrazine. In other embodiments, R₁ is pyridazine. In other
embodiments, R₁ is oxacyclobutane. In other embodiments, R₁ is 1-oxacyclobutane. In other
embodiments, R₁ is 2-oxacyclobutane. In other embodiments, R₁ is indole. In other embodiments, R₁ is
25 pyridine oxide. In other embodiments, R₁ is protonated pyridine oxide. In other embodiments, R₁ is
deprotonated pyridine oxide. In other embodiments, R₁ is 3-methyl-4H-1,2,4-triazole. In other
embodiments, R₁ is 5-methyl-1,2,4-oxadiazole. In other embodiments, R₁ is substituted or unsubstituted
aryl. In other embodiments, R₁ is phenyl. In other embodiments, R₁ is xylyl. In other embodiments, R₁
is 2,6-difluorophenyl. In other embodiments, R₁ is 4-fluoroxilyl. In other embodiments, R₁ is
30 bromophenyl. In other embodiments, R₁ is 2-bromophenyl. In other embodiments, R₁ is 3-bromophenyl.
In other embodiments, R₁ is 4-bromophenyl. In other embodiments, R₁ is substituted or unsubstituted
benzyl. In other embodiments, R₁ is 4-Cl-benzyl. In other embodiments, R₁ is 4-OH-benzyl. In other
embodiments, R₁ is benzyl. In other embodiments, R₁ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₁ is
CH₂-NH₂. In some embodiments, R₁ may be further substituted by at least one selected from: F, Cl, Br,
35 I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH
(e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅
linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g.,
OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈

cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

- 5 [0053] In some embodiments, **R₂** of formula **I-VIII** is H. In some embodiments, **R₂** is not H.
- [0054] In other embodiments, **R₂** of formula **I-VIII** is F. In other embodiments, **R₂** is Cl. In other embodiments, **R₂** is Br. In other embodiments, **R₂** is I. In other embodiments, **R₂** is OH. In other embodiments, **R₂** is R₈-(C₃-C₈ cycloalkyl). In other embodiments, **R₂** is CH₂-cyclohexyl. In other embodiments, **R₂** is R₈-(C₃-C₈ heterocyclic ring). In other embodiments, **R₂** is CH₂-morpholine. In other
- 10 embodiments, **R₂** is CH₂-imidazole. In other embodiments, **R₂** is CH₂-indazole. In other embodiments, **R₂** is CF₃. In other embodiments, **R₂** is CN. In other embodiments, **R₂** is CF₂CH₂CH₃. In other embodiments, **R₂** is CH₂CH₂CF₃. In other embodiments, **R₂** is CF₂CH(CH₃)₂. In other embodiments, **R₂** is CF(CH₃)-CH(CH₃)₂. In other embodiments, **R₂** is OCD₃. In other embodiments, **R₂** is NO₂. In other embodiments, **R₂** is NH₂. In other embodiments, **R₂** is NHR. In other embodiments, **R₂** is NH-CH₃. In
- 15 other embodiments, **R₂** is N(R)₂. In other embodiments, **R₂** is N(CH₃)₂. In other embodiments, **R₂** is R₈-N(R₁₀)(R₁₁). In other embodiments, **R₂** is CH₂-CH₂-N(CH₃)₂. In other embodiments, **R₂** is CH₂-NH₂. In other embodiments, **R₂** is CH₂-N(CH₃)₂. In other embodiments, **R₂** is R₉-R₈-N(R₁₀)(R₁₁). In other embodiments, **R₂** is C≡C-CH₂-NH₂. In other embodiments, **R₂** is B(OH)₂. In other embodiments, **R₂** is NHC(O)-R₁₀. In other embodiments, **R₂** is NHC(O)CH₃. In other embodiments, **R₂** is NHCO-
- 20 N(R₁₀)(R₁₁). In other embodiments, **R₂** is NHC(O)N(CH₃)₂. In other embodiments, **R₂** is COOH. In other embodiments, **R₂** is C(O)-R₁₀. In other embodiments, **R₂** is C(O)-CH₃. In other embodiments, **R₂** is C(O)O-R₁₀. In other embodiments, **R₂** is C(O)O-CH(CH₃)₂. In other embodiments, **R₂** is C(O)O-CH₃. In other embodiments, **R₂** is SO₂N(R₁₀)(R₁₁). In other embodiments, **R₂** is SO₂N(CH₃)₂. In other embodiments, **R₂** is SO₂NHC(O)CH₃. In other embodiments, **R₂** is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other embodiments, **R₂** is methyl. In other embodiments, **R₂** is ethyl. In other
- 25 embodiments, **R₂** is iso-propyl. In other embodiments, **R₂** is Bu. In other embodiments, **R₂** is t-Bu. In other embodiments, **R₂** is iso-butyl. In other embodiments, **R₂** is pentyl. In other embodiments, **R₂** is propyl. In other embodiments, **R₂** is benzyl. In other embodiments, **R₂** is C(H)(OH)-CH₃. In other embodiments, **R₂** is C₂-C₅ linear or branched, substituted or unsubstituted alkenyl. In other
- 30 embodiments, **R₂** is CH=C(Ph)₂. In other embodiments, **R₂** is 2-CH₂-C₆H₄-Cl. In other embodiments, **R₂** is 3-CH₂-C₆H₄-Cl. In other embodiments, **R₂** is 4-CH₂-C₆H₄-Cl. In other embodiments, **R₂** is ethyl. In other embodiments, **R₂** is iso-propyl. In other embodiments, **R₂** is t-Bu. In other embodiments, **R₂** is iso-butyl. In other embodiments, **R₂** is pentyl. In other embodiments, **R₂** is substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl). In other embodiments, **R₂** is substituted or unsubstituted
- 35 C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, **R₂** is substituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, **R₂** is O-(CH₂)₂-pyrrolidine. In other embodiments, **R₂** is unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, **R₂** is methoxy. In other embodiments, **R₂** is ethoxy. In other embodiments, **R₂** is propoxy.

In other embodiments, R₂ is isopropoxy. In other embodiments, R₂ is O-CH₂-cyclopropyl. In other embodiments, R₂ is O-cyclobutyl. In other embodiments, R₂ is O-cyclopentyl. In other embodiments, R₂ is O-cyclohexyl. In other embodiments, R₂ is O-1-oxacyclobutyl. In other embodiments, R₂ is O-2-oxacyclobutyl. In other embodiments, R₂ is 1-butoxy. In other embodiments, R₂ is 2-butoxy. In other

5 embodiments, R₂ is O-tBu. In other embodiments, R₂ is C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (O). In other embodiments, R₂ is O-1-oxacyclobutyl. In other embodiments, R₂ is O-2-oxacyclobutyl. In other embodiments, R₂ is C₁-C₅ linear or branched haloalkoxy. In other embodiments, R₂ is OCF₃. In other embodiments, R₂ is OCHF₂. In other embodiments, R₂ is substituted or unsubstituted C₃-C₈ cycloalkyl.

10 In other embodiments, R₂ is cyclopropyl. In other embodiments, R₂ is cyclopentyl. In other embodiments, R₂ is cyclohexyl. In other embodiments, R₂ is substituted or unsubstituted C₃-C₈ heterocyclic ring. In other embodiments, R₂ is morpholine. In other embodiments, R₂ is piperidine. In other embodiments, R₂ is piperazine. In other embodiments, R₂ is oxazole. In other embodiments, R₂ is methyl substituted oxazole. In other embodiments, R₂ is oxadiazole. In other embodiments, R₂ is methyl

15 substituted oxadiazole. In other embodiments, R₂ is imidazole. In other embodiments, R₂ is methyl substituted imidazole. In other embodiments, R₂ is pyridine. In other embodiments, R₂ is 2-pyridine. In other embodiments, R₂ is 3-pyridine. In other embodiments, R₂ is 3-methyl-2-pyridine. In other embodiments, R₂ is 4-pyridine. In other embodiments, R₂ is tetrazole. In other embodiments, R₂ is pyrimidine. In other embodiments, R₂ is pyrazine. In other embodiments, R₂ is pyridazine. In other

20 embodiments, R₂ is oxacyclobutane. In other embodiments, R₂ is 1-oxacyclobutane. In other embodiments, R₂ is 2-oxacyclobutane. In other embodiments, R₂ is indole. In other embodiments, R₂ is pyridine oxide. In other embodiments, R₂ is protonated pyridine oxide. In other embodiments, R₂ is deprotonated pyridine oxide. In other embodiments, R₂ is 3-methyl-4H-1,2,4-triazole. In other embodiments, R₂ is 5-methyl-1,2,4-oxadiazole. In other embodiments, R₂ is substituted or unsubstituted

25 aryl. In other embodiments, R₂ is phenyl. In other embodiments, R₂ is xylyl. In other embodiments, R₂ is 2,6-difluorophenyl. In other embodiments, R₂ is 4-fluorophenyl. In other embodiments, R₂ is bromophenyl. In other embodiments, R₂ is 2-bromophenyl. In other embodiments, R₂ is 3-bromophenyl. In other embodiments, R₂ is 4-bromophenyl. In other embodiments, R₂ is substituted or unsubstituted benzyl. In other embodiments, R₂ is 4-Cl-benzyl. In other embodiments, R₂ is 4-OH-benzyl. In other

30 embodiments, R₂ is benzyl. In other embodiments, R₂ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₂ is CH₂-NH₂. In other embodiments, R₂ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g.,

35 OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂),

dialkylphosphate (e.g., $\text{OP}(\text{O})(\text{OCH}_3)_2$), CN and NO_2 ; each is a separate embodiment according to this invention.

[0055] In some embodiments, R_1 and R_2 of formula **I-VIII** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring pyrrol ring. In some
 5 embodiments, R_1 and R_2 are joint together to form a 5 or 6 membered heterocyclic ring. In some
 embodiments, R_1 and R_2 are joint together to form a 6 membered substituted aliphatic heterocyclic ring.
 In some embodiments, R_1 and R_2 are joint together to form a 5 membered substituted aliphatic
 heterocyclic ring. In some embodiments, R_1 and R_2 are joint together to form a 5 or 6 membered
 unsubstituted, aliphatic heterocyclic ring. In some embodiments, R_1 and R_2 are joint together to form a
 10 [1,3]dioxole ring. In some embodiments, R_1 and R_2 are joint together to form a piperazine ring. In
 some embodiments, R_1 and R_2 are joint together to form a morpholine ring. In some embodiments, R_1
 and R_2 are joint together to form a 5 or 6 membered unsubstituted, aromatic heterocyclic ring. In some
 embodiments, R_1 and R_2 are joint together to form a pyrrol ring. In some embodiments, R_1 and R_2 are
 joint together to form a furanone ring (e.g., furan-2(3H)-one). In some embodiments, R_1 and R_2 are joint
 15 together to form a pyridine ring. In some embodiments, R_1 and R_2 are joint together to form a pyrazine
 ring. In some embodiments, R_1 and R_2 are joint together to form an imidazole ring. In some
 embodiments, R_1 and R_2 are joint together to form a 5 or 6 membered substituted or unsubstituted
 aromatic carbocyclic ring. In some embodiments, R_1 and R_2 are joint together to form a benzene ring. In
 some embodiments, R_1 and R_2 are joint together to form a cyclohexene ring.

20 [0056] In some embodiments, R_{20} of formula **I-IV**, **VIII** and/or **IX** is H. In some embodiments, R_{20} is not H.

[0057] In other embodiments, R_{20} of formula **I-IV**, **VIII** and/or **IX** is F. In other embodiments, R_{20} is Cl. In other embodiments, R_{20} is Br. In other embodiments, R_{20} is I. In other embodiments, R_{20} is OH. In other embodiments, R_{20} is R_8 -(C₃-C₈ cycloalkyl). In other embodiments, R_{20} is CH_2 -morpholine. In
 25 other embodiments, R_{20} is CH_2 -cyclohexyl. In other embodiments, R_{20} is R_8 -(C₃-C₈ heterocyclic ring).
 In other embodiments, R_{20} is CH_2 -imidazole. In other embodiments, R_{20} is CH_2 -indazole. In other
 embodiments, R_{20} is CF_3 . In other embodiments, R_{20} is CN. In other embodiments, R_{20} is $\text{CF}_2\text{CH}_2\text{CH}_3$.
 In other embodiments, R_{20} is $\text{CH}_2\text{CH}_2\text{CF}_3$. In other embodiments, R_{20} is $\text{CF}_2\text{CH}(\text{CH}_3)_2$. In other
 embodiments, R_{20} is $\text{CF}(\text{CH}_3)\text{-CH}(\text{CH}_3)_2$. In other embodiments, R_{20} is OCD_3 . In other embodiments,
 30 R_{20} is NO_2 . In other embodiments, R_{20} is NH_2 . In other embodiments, R_{20} is NHR. In other embodiments,
 R_{20} is NH-CH_3 . In other embodiments, R_{20} is N(R)_2 . In other embodiments, R_{20} is $\text{N(CH}_3)_2$. In other
 embodiments, R_{20} is $\text{R}_8\text{-N(R}_{10}\text{)(R}_{11}\text{)}$. In other embodiments, R_{20} is $\text{CH}_2\text{-CH}_2\text{-N(CH}_3)_2$. In other
 embodiments, R_{20} is $\text{CH}_2\text{-NH}_2$. In other embodiments, R_{20} is $\text{CH}_2\text{-N(CH}_3)_2$. In other embodiments, R_{20}
 is $\text{R}_9\text{-R}_8\text{-N(R}_{10}\text{)(R}_{11}\text{)}$. In other embodiments, R_{20} is $\text{C}\equiv\text{C-CH}_2\text{-NH}_2$. In other embodiments, R_{20} is
 35 B(OH)_2 . In other embodiments, R_{20} is NHC(O)-R_{10} . In other embodiments, R_{20} is NHC(O)CH_3 . In other
 embodiments, R_{20} is $\text{NHCO-N(R}_{10}\text{)(R}_{11}\text{)}$. In other embodiments, R_{20} is $\text{NHC(O)N(CH}_3)_2$. In other
 embodiments, R_{20} is COOH . In other embodiments, R_{20} is C(O)-R_{10} . In other embodiments, R_{20} is C(O)-CH_3 . In other
 embodiments, R_{20} is C(O)O-R_{10} . In other embodiments, R_{20} is $\text{C(O)O-CH(CH}_3)_2$. In other

embodiments, R₂₀ is C(O)O-CH₃. In other embodiments, R₂₀ is SO₂N(R₁₀)(R₁₁). In other embodiments, R₂₀ is SO₂N(CH₃)₂. In other embodiments, R₂₀ is SO₂NHC(O)CH₃. In other embodiments, R₂₀ is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other embodiments, R₂₀ is methyl. In other embodiments, R₂₀ is ethyl. In other embodiments, R₂₀ is iso-propyl. In other embodiments, R₂₀ is Bu. In other embodiments, R₂₀ is t-Bu. In other embodiments, R₂₀ is iso-butyl. In other embodiments, R₂₀ is pentyl. In other embodiments, R₂₀ is propyl. In other embodiments, R₂₀ is benzyl. In other embodiments, R₂₀ is C(H)(OH)-CH₃. In other embodiments, R₂₀ is C₂-C₅ linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R₂₀ is CH=C(Ph)₂. In other embodiments, R₂₀ is 2-CH₂-C₆H₄-Cl. In other embodiments, R₂₀ is 3-CH₂-C₆H₄-Cl. In other embodiments, R₂₀ is 4-CH₂-C₆H₄-Cl. In other embodiments, R₂₀ is ethyl. In other embodiments, R₂₀ is iso-propyl. In other embodiments, R₂₀ is t-Bu. In other embodiments, R₂₀ is iso-butyl. In other embodiments, R₂₀ is pentyl. In other embodiments, R₂₀ is substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl). In other embodiments, R₂₀ is substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₀ is substituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₀ is O-(CH₂)₂-pyrrolidine. In other embodiments, R₂₀ is unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₀ is methoxy. In other embodiments, R₂₀ is ethoxy. In other embodiments, R₂₀ is propoxy. In other embodiments, R₂₀ is isopropoxy. In other embodiments, R₂₀ is O-CH₂-cyclopropyl. In other embodiments, R₂₀ is O-cyclobutyl. In other embodiments, R₂₀ is O-cyclopentyl. In other embodiments, R₂₀ is O-cyclohexyl. In other embodiments, R₂₀ is O-1-oxacyclobutyl. In other embodiments, R₂₀ is O-2-oxacyclobutyl. In other embodiments, R₂₀ is 1-butoxy. In other embodiments, R₂₀ is 2-butoxy. In other embodiments, R₂₀ is O-tBu. In other embodiments, R₂₀ is C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (O). In other embodiments, R₂₀ is O-1-oxacyclobutyl. In other embodiments, R₂₀ is O-2-oxacyclobutyl. In other embodiments, R₂₀ is C₁-C₅ linear or branched haloalkoxy. In other embodiments, R₂₀ is OCF₃. In other embodiments, R₂₀ is OCHF₂. In other embodiments, R₂₀ is substituted or unsubstituted C₃-C₈ cycloalkyl. In other embodiments, R₂₀ is cyclopropyl. In other embodiments, R₂₀ is cyclopentyl. In other embodiments, R₂₀ is cyclohexyl. In other embodiments, R₂₀ is substituted or unsubstituted C₃-C₈ heterocyclic ring. In other embodiments, R₂₀ is morpholine. In other embodiments, R₂₀ is piperidine. In other embodiments, R₂₀ is piperazine. In other embodiments, R₂₀ is oxazole. In other embodiments, R₂₀ is methyl substituted oxazole. In other embodiments, R₂₀ is oxadiazole. In other embodiments, R₂₀ is methyl substituted oxadiazole. In other embodiments, R₂₀ is imidazole. In other embodiments, R₂₀ is methyl substituted imidazole. In other embodiments, R₂₀ is pyridine. In other embodiments, R₂₀ is 2-pyridine. In other embodiments, R₂₀ is 3-pyridine. In other embodiments, R₂₀ is 3-methyl-2-pyridine. In other embodiments, R₂₀ is 4-pyridine. In other embodiments, R₂₀ is tetrazole. In other embodiments, R₂₀ is pyrimidine. In other embodiments, R₂₀ is pyrazine. In other embodiments, R₂₀ is pyridazine. In other embodiments, R₂₀ is oxacyclobutane. In other embodiments, R₂₀ is 1-oxacyclobutane. In other embodiments, R₂₀ is 2-oxacyclobutane. In other embodiments, R₂₀ is indole. In other embodiments, R₂₀ is pyridine oxide. In other embodiments, R₂₀ is

protonated pyridine oxide. In other embodiments, R₂₀ is deprotonated pyridine oxide. In other embodiments, R₂₀ is 3-methyl-4H-1,2,4-triazole. In other embodiments, R₂₀ is 5-methyl-1,2,4-oxadiazole. In other embodiments, R₂₀ is substituted or unsubstituted aryl. In other embodiments, R₂₀ is phenyl. In other embodiments, R₂₀ is xylyl. In other embodiments, R₂₀ is 2,6-difluorophenyl. In other
5 embodiments, R₂₀ is 4-fluoroxilyl. In other embodiments, R₂₀ is bromophenyl. In other embodiments, R₂₀ is 2-bromophenyl. In other embodiments, R₂₀ is 3-bromophenyl. In other embodiments, R₂₀ is 4-bromophenyl. In other embodiments, R₂₀ is substituted or unsubstituted benzyl. In other embodiments, R₂₀ is 4-Cl-benzyl. In other embodiments, R₂₀ is 4-OH-benzyl. In other embodiments, R₂₀ is benzyl. In other
10 embodiments, R₂₀ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₂₀ is CH₂-NH₂. In other
embodiments, R₂₀ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g.,
15 cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

[0058] In some embodiments, R₂₁ of formula VIII and/or IX is H. In some embodiments, R₂₁ is not H.

[0059] In other embodiments, R₂₁ of formula VIII and/or IX is F. In other embodiments, R₂₁ is Cl. In
20 other embodiments, R₂₁ is Br. In other embodiments, R₂₁ is I. In other embodiments, R₂₁ is OH. In other
embodiments, R₂₁ is R₈-(C₃-C₈ cycloalkyl). In other embodiments, R₂₁ is CH₂-cyclohexyl. In other
embodiments, R₂₁ is R₈-(C₃-C₈ heterocyclic ring). In other embodiments, R₂₁ is CH₂-morpholine. In
other embodiments, R₂₁ is CH₂-imidazole. In other embodiments, R₂₁ is CH₂-indazole. In other
embodiments, R₂₁ is CF₃. In other embodiments, R₂₁ is CN. In other embodiments, R₂₁ is CF₂CH₂CH₃.
25 In other embodiments, R₂₁ is CH₂CH₂CF₃. In other embodiments, R₂₁ is CF₂CH(CH₃)₂. In other
embodiments, R₂₁ is CF(CH₃)-CH(CH₃)₂. In other embodiments, R₂₁ is OCD₃. In other embodiments,
R₂₁ is NO₂. In other embodiments, R₂₁ is NH₂. In other embodiments, R₂₁ is NHR. In other embodiments,
R₂₁ is NH-CH₃. In other embodiments, R₂₁ is N(R)₂. In other embodiments, R₂₁ is N(CH₃)₂. In other
embodiments, R₂₁ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₂₁ is CH₂-CH₂-N(CH₃)₂. In other
30 embodiments, R₂₁ is CH₂-NH₂. In other embodiments, R₂₁ is CH₂-N(CH₃)₂. In other embodiments, R₂₁
is R₉-R₈-N(R₁₀)(R₁₁). In other embodiments, R₂₁ is C≡C-CH₂-NH₂. In other embodiments, R₂₁ is
B(OH)₂. In other embodiments, R₂₁ is NHC(O)-R₁₀. In other embodiments, R₂₁ is NHC(O)CH₃. In other
embodiments, R₂₁ is NHCO-N(R₁₀)(R₁₁). In other embodiments, R₂₁ is NHC(O)N(CH₃)₂. In other
embodiments, R₂₁ is COOH. In other embodiments, R₂₁ is C(O)-R₁₀. In other embodiments, R₂₁ is C(O)-
35 CH₃. In other embodiments, R₂₁ is C(O)O-R₁₀. In other embodiments, R₂₁ is C(O)O-CH(CH₃)₂. In other
embodiments, R₂₁ is C(O)O-CH₃. In other embodiments, R₂₁ is SO₂N(R₁₀)(R₁₁). In other embodiments,
R₂₁ is SO₂N(CH₃)₂. In other embodiments, R₂₁ is SO₂NHC(O)CH₃. In other embodiments, R₂₁ is C₁-C₅
linear or branched, substituted or unsubstituted alkyl. In other embodiments, R₂₁ is methyl. In other

embodiments, R₂₁ is ethyl. In other embodiments, R₂₁ is iso-propyl. In other embodiments, R₂₁ is Bu. In other embodiments, R₂₁ is t-Bu. In other embodiments, R₂₁ is iso-butyl. In other embodiments, R₂₁ is pentyl. In other embodiments, R₂₁ is propyl. In other embodiments, R₂₁ is benzyl. In other embodiments, R₂₁ is C(H)(OH)-CH₃. In other embodiments, R₂₁ is C₂-C₅ linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R₂₁ is CH=C(Ph)₂. In other embodiments, R₂₁ is 2-CH₂-C₆H₄-Cl. In other embodiments, R₂₁ is 3-CH₂-C₆H₄-Cl. In other embodiments, R₂₁ is 4-CH₂-C₆H₄-Cl. In other embodiments, R₂₁ is ethyl. In other embodiments, R₂₁ is iso-propyl. In other embodiments, R₂₁ is t-Bu. In other embodiments, R₂₁ is iso-butyl. In other embodiments, R₂₁ is pentyl. In other embodiments, R₂₁ is substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl). In other embodiments, R₂₁ is substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₁ is substituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₁ is O-(CH₂)₂-pyrrolidine. In other embodiments, R₂₁ is unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₁ is methoxy. In other embodiments, R₂₁ is ethoxy. In other embodiments, R₂₁ is propoxy. In other embodiments, R₂₁ is isopropoxy. In other embodiments, R₂₁ is O-CH₂-cyclopropyl. In other embodiments, R₂₁ is O-cyclobutyl. In other embodiments, R₂₁ is O-cyclopentyl. In other embodiments, R₂₁ is O-cyclohexyl. In other embodiments, R₂₁ is O-1-oxacyclobutyl. In other embodiments, R₂₁ is O-2-oxacyclobutyl. In other embodiments, R₂₁ is 1-butoxy. In other embodiments, R₂₁ is 2-butoxy. In other embodiments, R₂₁ is O-tBu. In other embodiments, R₂₁ is C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (O). In other embodiments, R₂₁ is O-1-oxacyclobutyl. In other embodiments, R₂₁ is O-2-oxacyclobutyl. In other embodiments, R₂₁ is C₁-C₅ linear or branched haloalkoxy. In other embodiments, R₂₁ is OCF₃. In other embodiments, R₂₁ is OCHF₂. In other embodiments, R₂₁ is substituted or unsubstituted C₃-C₈ cycloalkyl. In other embodiments, R₂₁ is cyclopropyl. In other embodiments, R₂₁ is cyclopentyl. In other embodiments, R₂₁ is cyclohexyl. In other embodiments, R₂₁ is substituted or unsubstituted C₃-C₈ heterocyclic ring. In other embodiments, R₂₁ is morpholine. In other embodiments, R₂₁ is piperidine. In other embodiments, R₂₁ is piperazine. In other embodiments, R₂₁ is oxazole. In other embodiments, R₂₁ is methyl substituted oxazole. In other embodiments, R₂₁ is oxadiazole. In other embodiments, R₂₁ is methyl substituted oxadiazole. In other embodiments, R₂₁ is imidazole. In other embodiments, R₂₁ is methyl substituted imidazole. In other embodiments, R₂₁ is pyridine. In other embodiments, R₂₁ is 2-pyridine. In other embodiments, R₂₁ is 3-pyridine. In other embodiments, R₂₁ is 3-methyl-2-pyridine. In other embodiments, R₂₁ is 4-pyridine. In other embodiments, R₂₁ is tetrazole. In other embodiments, R₂₁ is pyrimidine. In other embodiments, R₂₁ is pyrazine. In other embodiments, R₂₁ is pyridazine. In other embodiments, R₂₁ is oxacyclobutane. In other embodiments, R₂₁ is 1-oxacyclobutane. In other embodiments, R₂₁ is 2-oxacyclobutane. In other embodiments, R₂₁ is indole. In other embodiments, R₂₁ is pyridine oxide. In other embodiments, R₂₁ is protonated pyridine oxide. In other embodiments, R₂₁ is deprotonated pyridine oxide. In other embodiments, R₂₁ is 3-methyl-4H-1,2,4-triazole. In other embodiments, R₂₁ is 5-methyl-1,2,4-oxadiazole. In other embodiments, R₂₁ is substituted or unsubstituted aryl. In other embodiments, R₂₁ is

phenyl. In other embodiments, R₂₁ is xylyl. In other embodiments, R₂₁ is 2,6-difluorophenyl. In other embodiments, R₂₁ is 4-fluorophenyl. In other embodiments, R₂₁ is bromophenyl. In other embodiments, R₂₁ is 2-bromophenyl. In other embodiments, R₂₁ is 3-bromophenyl. In other embodiments, R₂₁ is 4-bromophenyl. In other embodiments, R₂₁ is substituted or unsubstituted benzyl. In other embodiments, R₂₁ is 4-Cl-benzyl. In other embodiments, R₂₁ is 4-OH-benzyl. In other embodiments, R₂₁ is benzyl. In other embodiments, R₂₁ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₂₁ is CH₂-NH₂. In other embodiments, R₂₁ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

[0060] In some embodiments, R₂₂ of formula VIII and/or IX is H. In some embodiments, R₂₂ is not H. [0061] In other embodiments, R₂₂ of formula VIII and/or IX is F. In other embodiments, R₂₂ is Cl. In other embodiments, R₂₂ is Br. In other embodiments, R₂₂ is I. In other embodiments, R₂₂ is OH. In other embodiments, R₂₂ is R₈-(C₃-C₈ cycloalkyl). In other embodiments, R₂₂ is CH₂-morpholine. In other embodiments, R₂₂ is CH₂-cyclohexyl. In other embodiments, R₂₂ is R₈-(C₃-C₈ heterocyclic ring). In other embodiments, R₂₂ is CH₂-imidazole. In other embodiments, R₂₂ is CH₂-indazole. In other embodiments, R₂₂ is CF₃. In other embodiments, R₂₂ is CN. In other embodiments, R₂₂ is CF₂CH₂CH₃. In other embodiments, R₂₂ is CH₂CH₂CF₃. In other embodiments, R₂₂ is CF₂CH(CH₃)₂. In other embodiments, R₂₂ is CF(CH₃)-CH(CH₃)₂. In other embodiments, R₂₂ is OCD₃. In other embodiments, R₂₂ is NO₂. In other embodiments, R₂₂ is NH₂. In other embodiments, R₂₂ is NHR. In other embodiments, R₂₂ is NH-CH₃. In other embodiments, R₂₂ is N(R)₂. In other embodiments, R₂₂ is N(CH₃)₂. In other embodiments, R₂₂ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₂₂ is CH₂-CH₂-N(CH₃)₂. In other embodiments, R₂₂ is CH₂-NH₂. In other embodiments, R₂₂ is CH₂-N(CH₃)₂. In other embodiments, R₂₂ is R₉-R₈-N(R₁₀)(R₁₁). In other embodiments, R₂₂ is C≡C-CH₂-NH₂. In other embodiments, R₂₂ is B(OH)₂. In other embodiments, R₂₂ is NHC(O)-R₁₀. In other embodiments, R₂₂ is NHC(O)CH₃. In other embodiments, R₂₂ is NHCO-N(R₁₀)(R₁₁). In other embodiments, R₂₂ is NHC(O)N(CH₃)₂. In other embodiments, R₂₂ is COOH. In other embodiments, R₂₂ is C(O)-R₁₀. In other embodiments, R₂₂ is C(O)-CH₃. In other embodiments, R₂₂ is C(O)O-R₁₀. In other embodiments, R₂₂ is C(O)O-CH(CH₃)₂. In other embodiments, R₂₂ is C(O)O-CH₃. In other embodiments, R₂₂ is SO₂N(R₁₀)(R₁₁). In other embodiments, R₂₂ is SO₂N(CH₃)₂. In other embodiments, R₂₂ is SO₂NHC(O)CH₃. In other embodiments, R₂₂ is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other embodiments, R₂₂ is methyl. In other embodiments, R₂₂ is ethyl. In other embodiments, R₂₂ is iso-propyl. In other embodiments, R₂₂ is Bu. In other embodiments, R₂₂ is t-Bu. In other embodiments, R₂₂ is iso-butyl. In other embodiments, R₂₂ is pentyl. In other embodiments, R₂₂ is propyl. In other embodiments, R₂₂ is benzyl. In other embodiments,

R₂₂ is C(H)(OH)-CH₃. In other embodiments, R₂₂ is C₂-C₅ linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R₂₂ is CH=C(Ph)₂. In other embodiments, R₂₂ is 2-CH₂-C₆H₄-Cl. In other embodiments, R₂₂ is 3-CH₂-C₆H₄-Cl. In other embodiments, R₂₂ is 4-CH₂-C₆H₄-Cl. In other embodiments, R₂₂ is ethyl. In other embodiments, R₂₂ is iso-propyl. In other embodiments, R₂₂ is t-Bu. In other embodiments, R₂₂ is iso-butyl. In other embodiments, R₂₂ is pentyl. In other embodiments, R₂₂ is substituted or unsubstituted C₃-C₈ cycloalkyl (e.g., cyclopropyl, cyclopentyl). In other embodiments, R₂₂ is substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₂ is substituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₂ is O-(CH₂)₂-pyrrolidine. In other embodiments, R₂₂ is unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy. In other embodiments, R₂₂ is methoxy. In other embodiments, R₂₂ is ethoxy. In other embodiments, R₂₂ is propoxy. In other embodiments, R₂₂ is isopropoxy. In other embodiments, R₂₂ is O-CH₂-cyclopropyl. In other embodiments, R₂₂ is O-cyclobutyl. In other embodiments, R₂₂ is O-cyclopentyl. In other embodiments, R₂₂ is O-cyclohexyl. In other embodiments, R₂₂ is O-1-oxacyclobutyl. In other embodiments, R₂₂ is O-2-oxacyclobutyl. In other embodiments, R₂₂ is 1-butoxy. In other embodiments, R₂₂ is 2-butoxy. In other embodiments, R₂₂ is O-tBu. In other embodiments, R₂₂ is C₁-C₅ linear or branched or C₃-C₈ cyclic alkoxy wherein at least one methylene group (CH₂) in the alkoxy is replaced with an oxygen atom (O). In other embodiments, R₂₂ is O-1-oxacyclobutyl. In other embodiments, R₂₂ is O-2-oxacyclobutyl. In other embodiments, R₂₂ is C₁-C₅ linear or branched haloalkoxy. In other embodiments, R₂₂ is OCF₃. In other embodiments, R₂₂ is OCHF₂. In other embodiments, R₂₂ is substituted or unsubstituted C₃-C₈ cycloalkyl. In other embodiments, R₂₂ is cyclopropyl. In other embodiments, R₂₂ is cyclopentyl. In other embodiments, R₂₂ is cyclohexyl. In other embodiments, R₂₂ is substituted or unsubstituted C₃-C₈ heterocyclic ring. In other embodiments, R₂₂ is morpholine. In other embodiments, R₂₂ is piperidine. In other embodiments, R₂₂ is piperazine. In other embodiments, R₂₂ is oxazole. In other embodiments, R₂₂ is methyl substituted oxazole. In other embodiments, R₂₂ is oxadiazole. In other embodiments, R₂₂ is methyl substituted oxadiazole. In other embodiments, R₂₂ is imidazole. In other embodiments, R₂₂ is methyl substituted imidazole. In other embodiments, R₂₂ is pyridine. In other embodiments, R₂₂ is 2-pyridine. In other embodiments, R₂₂ is 3-pyridine. In other embodiments, R₂₂ is 3-methyl-2-pyridine. In other embodiments, R₂₂ is 4-pyridine. In other embodiments, R₂₂ is tetrazole. In other embodiments, R₂₂ is pyrimidine. In other embodiments, R₂₂ is pyrazine. In other embodiments, R₂₂ is pyridazine. In other embodiments, R₂₂ is oxacyclobutane. In other embodiments, R₂₂ is 1-oxacyclobutane. In other embodiments, R₂₂ is 2-oxacyclobutane. In other embodiments, R₂₂ is indole. In other embodiments, R₂₂ is pyridine oxide. In other embodiments, R₂₂ is protonated pyridine oxide. In other embodiments, R₂₂ is deprotonated pyridine oxide. In other embodiments, R₂₂ is 3-methyl-4H-1,2,4-triazole. In other embodiments, R₂₂ is 5-methyl-1,2,4-oxadiazole. In other embodiments, R₂₂ is substituted or unsubstituted aryl. In other embodiments, R₂₂ is phenyl. In other embodiments, R₂₂ is xylyl. In other embodiments, R₂₂ is 2,6-difluorophenyl. In other embodiments, R₂₂ is 4-fluorophenyl. In other embodiments, R₂₂ is bromophenyl. In other embodiments, R₂₂ is 2-bromophenyl. In other embodiments, R₂₂ is 3-bromophenyl. In other embodiments, R₂₂ is 4-

bromophenyl. In other embodiments, R₂₂ is substituted or unsubstituted benzyl. In other embodiments, R₂₂ is 4-Cl-benzyl. In other embodiments, R₂₂ is 4-OH-benzyl. In other embodiments, R₂₂ is benzyl. In other embodiments, R₂₂ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₂₂ is CH₂-NH₂. In other embodiments, R₂₂ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

[0062] In some embodiments, R₁ and R₂₁ of formula **VIII** and/or **IX** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring pyrrol ring. In some embodiments, R₁ and R₂₁ are joint together to form a 5 or 6 membered heterocyclic ring.

15 In some embodiments, R₁ and R₂₁ are joint together to form a 6 membered substituted aliphatic heterocyclic ring. In some embodiments, R₁ and R₂₁ are joint together to form a 5 membered substituted aliphatic heterocyclic ring. In some embodiments, R₁ and R₂₁ are joint together to form a 5 or 6 membered unsubstituted, aliphatic heterocyclic ring. In some embodiments, R₁ and R₂₁ are joint together to form a [1,3]dioxole ring. In some embodiments, R₁ and R₂₁ are joint together to form a piperazine ring.

20 In some embodiments, R₁ and R₂₁ are joint together to form a morpholine ring. In some embodiments, R₁ and R₂₁ are joint together to form a 5 or 6 membered unsubstituted, aromatic heterocyclic ring. In some embodiments, R₁ and R₂₁ are joint together to form a pyrrol ring. In some embodiments, R₁ and R₂₁ are joint together to form a furanone ring (e.g., furan-2(3H)-one). In some embodiments, R₁ and R₂₁ are joint together to form a pyridine ring. In some embodiments, R₁ and R₂₁ are joint together to form a pyrazine ring.

25 In some embodiments, R₁ and R₂₁ are joint together to form an imidazole ring. In some embodiments, R₁ and R₂₁ are joint together to form a 5 or 6 membered substituted or unsubstituted aromatic carbocyclic ring. In some embodiments, R₁ and R₂₁ are joint together to form a benzene ring. In some embodiments, R₁ and R₂₁ are joint together to form a cyclohexene ring.

[0063] In some embodiments, R₂₁ and R₂₂ of formula **VIII** and/or **IX** are joint together to form a 5 or 6 membered substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring pyrrol ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a 5 or 6 membered heterocyclic ring.

30 In some embodiments, R₂₁ and R₂₂ are joint together to form a 6 membered substituted aliphatic heterocyclic ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a 5 membered substituted aliphatic heterocyclic ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a 5 or 6 membered unsubstituted, aliphatic heterocyclic ring. In some embodiments, R₁ and R₂₁ are joint together to form a [1,3]dioxole ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a piperazine ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a morpholine ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a 5 or 6 membered unsubstituted, aromatic

heterocyclic ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a pyrrol ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a furanone ring (e.g., furan-2(3H)-one). In some embodiments, R₂₁ and R₂₂ are joint together to form a pyridine ring. In some embodiments, R₂₁ and R₂₂ are joined together to form a pyrazine ring. In some embodiments, R₂₁ and R₂₂ are joined together to form an imidazole ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a 5 or 6 membered substituted or unsubstituted aromatic carbocyclic ring. In some embodiments, R₂₁ and R₂₂ are joint together to form a benzene ring. In some embodiments, R₂₁ and R₂₂ are joined together to form a cyclohexene ring.

[0064] In some embodiments, **R₂₀₁** of formula **IX** is H. In some embodiments, **R₂₀₁** is not H. In other embodiments, R₂₀₁ is F. In other embodiments, R₂₀₁ is Cl. In other embodiments, R₂₀₁ is Br. In other embodiments, R₂₀₁ is I. In other embodiments, R₂₀₁ is CF₃. In other embodiments, R₂₀₁ is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other embodiments, R₂₀₁ is C₁-C₅ linear substituted or unsubstituted alkyl. In other embodiments, R₂₀₁ is C₁-C₅ linear unsubstituted alkyl. In other embodiments, R₂₀₁ is C₁-C₅ a branched, unsubstituted alkyl. In other embodiments, R₂₀₁ is C₁-C₅ branched, substituted alkyl. In other embodiments, R₂₀₁ is methyl. In other embodiments, R₂₀₁ is ethyl. In other embodiments, R₂₀₁ is propyl. In other embodiments, R₂₀₁ is iso-propyl. In other embodiments, R₂₀₁ is t-Bu. In other embodiments, R₂₀₁ is iso-butyl. In other embodiments, R₂₀₁ is pentyl.

[0065] In some embodiments, **R₂₀₂** of formula **IX** is H. In some embodiments, **R₂₀₂** is not H. In other embodiments, R₂₀₂ is F. In other embodiments, R₂₀₂ is Cl. In other embodiments, R₂₀₂ is Br. In other embodiments, R₂₀₂ is I. In other embodiments, R₂₀₂ is CF₃. In other embodiments, R₂₀₂ is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other embodiments, R₂₀₂ is C₁-C₅ linear substituted or unsubstituted alkyl. In other embodiments, R₂₀₂ is C₁-C₅ linear unsubstituted alkyl. In other embodiments, R₂₀₂ is C₁-C₅ a branched, unsubstituted alkyl. In other embodiments, R₂₀₂ is C₁-C₅ branched, substituted alkyl. In other embodiments, R₂₀₂ is methyl. In other embodiments, R₂₀₂ is ethyl. In other embodiments, R₂₀₂ is propyl. In other embodiments, R₂₀₂ is iso-propyl. In other embodiments, R₂₀₂ is t-Bu. In other embodiments, R₂₀₂ is iso-butyl. In other embodiments, R₂₀₂ is pentyl.

[0066] In some embodiments, **R₃** of formula **I-IX** is H. In some embodiments, **R₃** is not H. In other embodiments, R₃ is Cl. In other embodiments, R₃ is I. In other embodiments, R₃ is F. In other embodiments, R₃ is Br. In other embodiments, R₃ is OH. In other embodiments, R₃ is CD₃. In other embodiments, R₃ is OCD₃. In other embodiments, R₃ is R₈-OH. In other embodiments, R₃ is CH₂-OH. In other embodiments, R₃ is -R₈-O-R₁₀. In other embodiments, R₃ is CH₂-O-CH₃. In other embodiments, R₃ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₃ is CH₂-NH₂. In other embodiments, R₃ is CH₂-N(CH₃)₂. In other embodiments, R₃ is COOH. In other embodiments, R₃ is C(O)O-R₁₀. In other embodiments, R₃ is C(O)O-CH₂CH₃. In other embodiments, R₃ is R₈-C(O)-R₁₀. In other embodiments, R₃ is CH₂C(O)CH₃. In other embodiments, R₃ is C(O)-R₁₀. In other embodiments, R₃ is C(O)-CH₃. In other embodiments, R₃ is C(O)-CH₂CH₃. In other embodiments, R₃ is C(O)-CH₂CH₂CH₃. In other embodiments, R₃ is C₁-C₅ linear or branched C(O)-haloalkyl. In other embodiments, R₃ is C(O)-CF₃. In other embodiments, R₃ is C(O)NH₂. In other embodiments, R₃ is C(O)NHR. In other embodiments, R₃ is C(O)NH(CH₃). In

other embodiments, R_3 is $C(O)N(R_{10})(R_{11})$. In other embodiments, R_3 is $C(O)N(CH_3)_2$. In other embodiments, R_3 is $C(O)N(CH_3)(CH_2CH_3)$. In other embodiments, R_3 is $C(O)N(CH_3)(CH_2CH_2-O-CH_3)$. In other embodiments, R_3 is $C(S)N(R_{10})(R_{11})$. In other embodiments, R_3 is $C(S)NH(CH_3)$. In other embodiments, R_3 is $C(O)$ -pyrrolidine. In other embodiments, R_3 is $C(O)$ -azetidine. In other

5 embodiments, R_3 is $C(O)$ -methylpiperazine. In other embodiments, R_3 is $C(O)$ -piperidine. In other embodiments, R_3 is $C(O)$ -morpholine. In other embodiments, R_3 is SO_2R . In other embodiments, R_3 is $SO_2N(R_{10})(R_{11})$. In other embodiments, R_3 is $SO_2NH(CH_3)$. In other embodiments, R_3 is $SO_2N(CH_3)_2$. In other embodiments, R_3 is C_1 - C_5 linear or branched, substituted or unsubstituted alkyl. In other

10 embodiments, R_3 is methyl. In other embodiments, R_3 is $C(OH)(CH_3)(Ph)$. In other embodiments, R_3 is ethyl. In other embodiments, R_3 is propyl. In other embodiments, R_3 is iso-propyl. In other embodiments, R_3 is *t*-Bu. In other embodiments, R_3 is iso-butyl. In other embodiments, R_3 is pentyl. In other

embodiments, R_3 is substituted or unsubstituted C_1 - C_5 linear or branched or C_3 - C_8 cyclic haloalkyl. In other embodiments, R_3 is CF_3 . In other embodiments, R_3 is CF_2CH_3 . In other embodiments, R_3 is CF_2 -cyclobutyl. In other embodiments, R_3 is CF_2 -cyclopropyl. In other embodiments, R_3 is CF_2 -methylcyclopropyl. In other embodiments, R_3 is $CF_2CH_2CH_3$. In other embodiments, R_3 is CH_2CF_3 . In other

15 embodiments, R_3 is CF_3 . In other embodiments, R_3 is $CF_2CH_2CH_3$. In other embodiments, R_3 is $CH_2CH_2CF_3$. In other embodiments, R_3 is $CF_2CH(CH_3)_2$. In other embodiments, R_3 is $CF(CH_3)-CH(CH_3)_2$. In other embodiments, R_3 is $C(OH)_2CF_3$. In other embodiments, R_3 is cyclopropyl- CF_3 . In other

embodiments, R_3 is C_1 - C_5 linear, branched or cyclic alkoxy. In other embodiments, R_3 is methoxy. In other

20 embodiments, R_3 is isopropoxy. In other embodiments, R_3 is substituted or unsubstituted C_3 - C_8 cycloalkyl. In other embodiments, R_3 is CF_3 -cyclopropyl. In other embodiments, R_3 is cyclopropyl. In other

embodiments, R_3 is cyclopentyl. In other embodiments, R_3 is substituted or unsubstituted C_3 - C_8 heterocyclic ring. In other embodiments, R_3 is oxadiazole. In other embodiments, R_3 is pyrrol. In other

embodiments, R_3 is *N*-methyloxetane-3-amine. In other embodiments, R_3 is thiophene. In other

25 embodiments, R_3 is oxazole. In other embodiments, R_3 is isoxazole. In other embodiments, R_3 is imidazole. In other embodiments, R_3 is furane. In other embodiments, R_3 is triazole. In other

embodiments, R_3 is methyl-triazole. In other embodiments, R_3 is pyridine. In other embodiments, R_3 is 2-pyridine. In other embodiments, R_3 is 3-pyridine. In other embodiments, R_3 is 4-pyridine. In other

embodiments, R_3 is pyrimidine. In other embodiments, R_3 is pyrazine. In other embodiments, R_3 is

30 oxacyclobutane. In other embodiments, R_3 is 1-oxacyclobutane. In other embodiments, R_3 is 2-oxacyclobutane. In other embodiments, R_3 is indole. In other embodiments, R_3 is 3-methyl-4H-1,2,4-triazole. In other

embodiments, R_3 is 5-methyl-1,2,4-oxadiazole. In other embodiments, R_3 is substituted or unsubstituted aryl. In other embodiments, R_3 is phenyl. In other embodiments, R_3 is $CH(CF_3)(NH-R_{10})$. In some

embodiments, R_3 may be further substituted by at least one selected from: F, Cl, Br, I, OH, C_1 - C_5 linear or branched alkyl (e.g. methyl, ethyl, propyl), C_1 - C_5 linear or branched alkyl-OH (e.g., $C(CH_3)_2CH_2-OH$, CH_2CH_2-OH), C_2 - C_5 linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C_2 - C_5 linear or branched, substituted or unsubstituted alkynyl (e.g., $CH\equiv C-CH_3$), OH, alkoxy, ester (e.g., $OC(O)-CH_3$), $N(R)_2$, CF_3 , aryl, phenyl, R_8 -aryl (e.g., CH_2CH_2-Ph), heteroaryl (e.g., imidazole) C_3 - C_8 cycloalkyl

(e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

- [0067] In some embodiments, **R₄** of formula **I-V** is H. In some embodiments, **R₄** is not H. In other
 5 embodiments, **R₄** is Cl. In other embodiments, **R₄** is I. In other embodiments, **R₄** is F. In other
 embodiments, **R₄** is Br. In other embodiments, **R₄** is OH. In other embodiments, **R₄** is CD₃. In other
 embodiments, **R₄** is OCD₃. In other embodiments, **R₄** is R₈-OH. In other embodiments, **R₄** is CH₂-OH.
 In other embodiments, **R₄** is -R₈-O-R₁₀. In other embodiments, **R₄** is CH₂-O-CH₃. In other embodiments,
R₄ is R₈-N(R₁₀)(R₁₁). In other embodiments, **R₄** is CH₂-NH₂. In other embodiments, **R₄** is CH₂-N(CH₃)₂.
 10 In other embodiments, **R₄** is COOH. In other embodiments, **R₄** is C(O)O-R₁₀. In other embodiments, **R₄**
 is C(O)O-CH₂CH₃. In other embodiments, **R₄** is R₈-C(O)-R₁₀. In other embodiments, **R₄** is CH₂C(O)CH₃.
 In other embodiments, **R₄** is C(O)-R₁₀. In other embodiments, **R₄** is C(O)-CH₃. In other embodiments,
R₄ is C(O)-CH₂CH₃. In other embodiments, **R₄** is C(O)-CH₂CH₂CH₃. In other embodiments, **R₄** is C₁-
 C₅ linear or branched C(O)-haloalkyl. In other embodiments, **R₄** is C(O)-CF₃. In other embodiments, **R₄**
 15 is C(O)NH₂. In other embodiments, **R₄** is C(O)NHR. In other embodiments, **R₄** is C(O)NH(CH₃). In
 other embodiments, **R₄** is C(O)N(R₁₀)(R₁₁). In other embodiments, **R₄** is C(O)N(CH₃)₂. In other
 embodiments, **R₄** is C(O)N(CH₃)(CH₂CH₃). In other embodiments, **R₄** is C(O)N(CH₃)(CH₂CH₂-O-CH₃).
 In other embodiments, **R₄** is C(S)N(R₁₀)(R₁₁). In other embodiments, **R₄** is C(S)NH(CH₃). In other
 embodiments, **R₄** is C(O)-pyrrolidine. In other embodiments, **R₄** is C(O)-azetidine. In other
 20 embodiments, **R₄** is C(O)-methylpiperazine. In other embodiments, **R₄** is C(O)-piperidine. In other
 embodiments, **R₄** is C(O)-morpholine. In other embodiments, **R₄** is SO₂R. In other embodiments, **R₄** is
 SO₂N(R₁₀)(R₁₁). In other embodiments, **R₄** is SO₂NH(CH₃). In other embodiments, **R₄** is SO₂N(CH₃)₂.
 In other embodiments, **R₄** is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other
 embodiments, **R₄** is methyl. In other embodiments, **R₄** is C(OH)(CH₃)(Ph). In other embodiments, **R₄** is
 25 ethyl. In other embodiments, **R₄** is propyl. In other embodiments, **R₄** is iso-propyl. In other embodiments,
R₄ is t-Bu. In other embodiments, **R₄** is iso-butyl. In other embodiments, **R₄** is pentyl. In other
 embodiments, **R₄** is substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl. In
 other embodiments, **R₄** is CF₃. In other embodiments, **R₄** is CF₂CH₃. In other embodiments, **R₄** is CF₂-
 cyclobutyl. In other embodiments, **R₄** is CF₂-cyclopropyl. In other embodiments, **R₄** is CF₂-
 30 methylcyclopropyl. In other embodiments, **R₄** is CF₂CH₂CH₃. In other embodiments, **R₄** is CH₂CF₃. In
 other embodiments, **R₄** is CF₃. In other embodiments, **R₄** is CF₂CH₂CH₃. In other embodiments, **R₄** is
 CH₂CH₂CF₃. In other embodiments, **R₄** is CF₂CH(CH₃)₂. In other embodiments, **R₄** is CF(CH₃)-
 CH(CH₃)₂. In other embodiments, **R₄** is C(OH)₂CF₃. In other embodiments, **R₄** is cyclopropyl-CF₃. In
 other embodiments, **R₄** is C₁-C₅ linear, branched or cyclic alkoxy. In other embodiments, **R₄** is methoxy.
 35 In other embodiments, **R₄** is isopropoxy. In other embodiments, **R₄** is substituted or unsubstituted C₃-C₈
 cycloalkyl. In other embodiments, **R₄** is CF₃-cyclopropyl. In other embodiments, **R₄** is cyclopropyl. In
 other embodiments, **R₄** is cyclopentyl. In other embodiments, **R₄** is substituted or unsubstituted C₃-C₈
 heterocyclic ring. In other embodiments, **R₄** is oxadiazole. In other embodiments, **R₄** is pyrrol. In other

embodiments, R₄ is thiophene. In other embodiments, R₄ is oxazole. In other embodiments, R₄ is isoxazole. In other embodiments, R₄ is imidazole. In other embodiments, R₄ is furane. In other embodiments, R₄ is triazole. In other embodiments, R₄ is methyl-triazole. In other embodiments, R₄ is pyridine. In other embodiments, R₄ is 2-pyridine. In other embodiments, R₄ is 3-pyridine. In other
 5 embodiments, R₄ is 4-pyridine. In other embodiments, R₄ is pyrimidine. In other embodiments, R₄ is pyrazine. In other embodiments, R₄ is oxacyclobutane. In other embodiments, R₄ is 1-oxacyclobutane. In other embodiments, R₄ is 2-oxacyclobutane. In other embodiments, R₄ is indole. In other
 10 embodiments, R₄ is 3-methyl-4H-1,2,4-triazole. In other embodiments, R₄ is 5-methyl-1,2,4-oxadiazole. In other embodiments, R₄ is substituted or unsubstituted aryl. In other embodiments, R₄ is phenyl. In
 other embodiments, R₄ is CH(CF₃)(NH-R₁₀). In some embodiments, R₄ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-
 C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-
 15 CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph),
 heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-
 phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate
 embodiment according to this invention.

[0068] In some embodiments, R₃ and R₄ of formula **I-V** are joint together to form a 5 or 6 membered
 20 substituted or unsubstituted, aliphatic or aromatic, carbocyclic or heterocyclic ring. In some
 embodiments, **R₃** and **R₄** are joint together to form a 5 or 6 membered carbocyclic ring. In some
 embodiments, R₃ and R₄ are joined together to form a 5 or 6 membered heterocyclic ring. In some
 embodiments, R₃ and R₄ are joined together to form a dioxole ring. [1,3]dioxole ring. In some
 embodiments, R₃ and R₄ are joined together to form a dihydrofuran-2(3H)-one ring. In some
 25 embodiments, R₃ and R₄ are joined together to form a furan-2(3H)-one ring. In some embodiments, R₃
 and R₄ are joined together to form a benzene ring. In some embodiments, R₃ and R₄ are joint together
 to form an imidazole ring. In some embodiments, R₃ and R₄ are joined together to form a pyridine ring. In
 some embodiments, R₃ and R₄ are joined together to form a pyrrole ring. In some embodiments, R₃ and
 R₄ are joined together to form a cyclohexene ring. In some embodiments, R₃ and R₄ are joined together
 30 to form a cyclopentene ring. In some embodiments, R₄ and R₃ are joint together to form a dioxepine ring.

[0069] In some embodiments, **R₄₀** of formula **I-IV** is H. In some embodiments, **R₄₀** is not H. In other
 embodiments, R₄₀ is Cl. In other embodiments, R₄₀ is I. In other embodiments, R₄₀ is F. In other
 embodiments, R₄₀ is Br. In other embodiments, R₄₀ is OH. In other embodiments, R₄₀ is CD₃. In other
 embodiments, R₄₀ is OCD₃. In other embodiments, R₄₀ is R₈-OH. In other embodiments, R₄₀ is CH₂-OH.
 35 In other embodiments, R₄₀ is -R₈-O-R₁₀. In other embodiments, R₄₀ is CH₂-O-CH₃. In other
 embodiments, R₄₀ is R₈-N(R₁₀)(R₁₁). In other embodiments, R₄₀ is CH₂-NH₂. In other embodiments, R₄₀
 is CH₂-N(CH₃)₂. In other embodiments, R₄₀ is COOH. In other embodiments, R₄₀ is C(O)O-R₁₀. In other
 embodiments, R₄₀ is C(O)O-CH₂CH₃. In other embodiments, R₄₀ is R₈-C(O)-R₁₀. In other embodiments,

R₄₀ is CH₂C(O)CH₃. In other embodiments, R₄₀ is C(O)-R₁₀. In other embodiments, R₄₀ is C(O)-CH₃. In other embodiments, R₄₀ is C(O)-CH₂CH₃. In other embodiments, R₄₀ is C(O)-CH₂CH₂CH₃. In other embodiments, R₄₀ is C₁-C₅ linear or branched C(O)-haloalkyl. In other embodiments, R₄₀ is C(O)-CF₃. In other embodiments, R₄₀ is C(O)NH₂. In other embodiments, R₄₀ is C(O)NHR. In other embodiments, R₄₀ is C(O)NH(CH₃). In other embodiments, R₄₀ is C(O)N(R₁₀)(R₁₁). In other embodiments, R₄₀ is C(O)N(CH₃)₂. In other embodiments, R₄₀ is C(O)N(CH₃)(CH₂CH₃). In other embodiments, R₄₀ is C(O)N(CH₃)(CH₂CH₂-O-CH₃). In other embodiments, R₄₀ is C(S)N(R₁₀)(R₁₁). In other embodiments, R₄₀ is C(S)NH(CH₃). In other embodiments, R₄₀ is C(O)-pyrrolidine. In other embodiments, R₄₀ is C(O)-azetidine. In other embodiments, R₄₀ is C(O)-methylpiperazine. In other embodiments, R₄₀ is C(O)-piperidine. In other embodiments, R₄₀ is C(O)-morpholine. In other embodiments, R₄₀ is SO₂R. In other embodiments, R₄₀ is SO₂N(R₁₀)(R₁₁). In other embodiments, R₄₀ is SO₂NH(CH₃). In other embodiments, R₄₀ is SO₂N(CH₃)₂. In other embodiments, R₄₀ is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other embodiments, R₄₀ is methyl. In other embodiments, R₄₀ is C(OH)(CH₃)(Ph). In other embodiments, R₄₀ is ethyl. In other embodiments, R₄₀ is propyl. In other embodiments, R₄₀ is iso-propyl. In other embodiments, R₄₀ is t-Bu. In other embodiments, R₄₀ is iso-butyl. In other embodiments, R₄₀ is pentyl. In other embodiments, R₄₀ is substituted or unsubstituted C₁-C₅ linear or branched or C₃-C₈ cyclic haloalkyl. In other embodiments, R₄₀ is CF₂CH₃. In other embodiments, R₄₀ is CF₂-cyclobutyl. In other embodiments, R₄₀ is CF₂-cyclopropyl. In other embodiments, R₄₀ is CF₂-methylcyclopropyl. In other embodiments, R₄₀ is CF₂CH₂CH₃. In other embodiments, R₄₀ is CH₂CF₃. In other embodiments, R₄₀ is CF₃. In other embodiments, R₄₀ is CF₂CH₂CH₃. In other embodiments, R₄₀ is CH₂CH₂CF₃. In other embodiments, R₄₀ is CF₂CH(CH₃)₂. In other embodiments, R₄₀ is CF(CH₃)-CH(CH₃)₂. In other embodiments, R₄₀ is C(OH)₂CF₃. In other embodiments, R₄₀ is cyclopropyl-CF₃. In other embodiments, R₄₀ is C₁-C₅ linear, branched or cyclic alkoxy. In other embodiments, R₄₀ is methoxy. In other embodiments, R₄₀ is isopropoxy. In other embodiments, R₄₀ is substituted or unsubstituted C₃-C₈ cycloalkyl. In other embodiments, R₄₀ is CF₃-cyclopropyl. In other embodiments, R₄₀ is cyclopropyl. In other embodiments, R₄₀ is cyclopentyl. In other embodiments, R₄₀ is substituted or unsubstituted C₃-C₈ heterocyclic ring. In other embodiments, R₄₀ is oxadiazole. In other embodiments, R₄₀ is pyrrol. In other embodiments, R₄₀ is thiophene. In other embodiments, R₄₀ is oxazole. In other embodiments, R₄₀ is isoxazole. In other embodiments, R₄₀ is imidazole. In other embodiments, R₄₀ is furane. In other embodiments, R₄₀ is triazole. In other embodiments, R₄₀ is methyl-triazole. In other embodiments, R₄₀ is pyridine. In other embodiments, R₄₀ is 2-pyridine. In other embodiments, R₄₀ is 3-pyridine. In other embodiments, R₄₀ is 4-pyridine. In other embodiments, R₄₀ is pyrimidine. In other embodiments, R₄₀ is pyrazine. In other embodiments, R₄₀ is oxacyclobutane. In other embodiments, R₄₀ is 1-oxacyclobutane. In other embodiments, R₄₀ is 2-oxacyclobutane. In other embodiments, R₄₀ is indole. In other embodiments, R₄₀ is 3-methyl-4H-1,2,4-triazole. In other embodiments, R₄₀ is 5-methyl-1,2,4-oxadiazole. In other embodiments, R₄₀ is substituted or unsubstituted aryl. In other embodiments, R₄₀ is phenyl. In other embodiments, R₄₀ is CH(CF₃)(NH-R₁₀). In some embodiments, R₄₀ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl,

ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

[0070] In some embodiments, **R₅** of formula **I-III** is H. In some embodiments, **R₅** is not H. In other embodiments, R₅ is C₁-C₅ linear or branched, substituted or unsubstituted alkyl. In other embodiments, R₅ is methyl. In other embodiments, R₅ is CH₂SH. In other embodiments, R₅ is ethyl. In other embodiments, R₅ is iso-propyl. In other embodiments, R₅ is CH₂SH. In other embodiments, R₅ is C₂-C₅ linear or branched, substituted or unsubstituted alkenyl. In other embodiments, R₅ is C₂-C₅ linear or branched, substituted or unsubstituted alkynyl. In other embodiments, R₅ is C(CH₃). In other embodiments, R₅ is C₁-C₅ linear or branched haloalkyl. In other embodiments, R₅ is CF₂CH₃. In other embodiments, R₅ is CH₂CF₃. In other embodiments, R₅ is CF₂CH₂CH₃. In other embodiments, R₅ is CF₃. In other embodiments, R₅ is CF₂CH₂CH₃. In other embodiments, R₅ is CH₂CH₂CF₃. In other embodiments, R₅ is CF₂CH(CH₃)₂. In other embodiments, R₅ is CF(CH₃)-CH(CH₃)₂. In other embodiments, R₅ is R₈-aryl. In other embodiments, R₅ is CH₂-Ph (i.e., benzyl). In other embodiments, R₅ is substituted or unsubstituted aryl. In other embodiments, R₅ is phenyl. In other embodiments, R₅ is substituted or unsubstituted heteroaryl. In other embodiments, R₅ is pyridine. In other embodiments, R₅ is 2-pyridine. In other embodiments, R₅ is 3-pyridine. In other embodiments, R₅ is 4-pyridine. In some embodiments, R₅ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

[0071] In some embodiments, **R₆** of formula **I-III** is H. In some embodiments, **R₆** is not H. In other embodiments, R₆ is C₁-C₅ linear or branched alkyl. In other embodiments, R₆ is methyl. In some embodiments, R₆ is ethyl. In some embodiments, R₆ is C(O)R wherein R is C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched alkoxy, phenyl, aryl or heteroaryl. In some embodiments, R₆ is S(O)₂R wherein R is C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched alkoxy, phenyl, aryl or heteroaryl.

[0072] In some embodiments, **R₆₀** of formula **I-III** is H. In some embodiments, **R₆₀** is not H. In other embodiments, R₆₀ is substituted or unsubstituted C₁-C₅ linear or branched alkyl. In other embodiments, R₆₀ is methyl. In some embodiments, R₆₀ is ethyl. In other embodiments, R₆₀ is substituted C₁-C₅ linear or branched alkyl. In other embodiments, R₆₀ is CH₂-OC(O)CH₃. In other embodiments, R₆₀ is CH₂-

PO₄H₂. In other embodiments, R₆₀ is CH₂-PO₄H-tBu. In other embodiments, R₆₀ is CH₂-OP(O)(OCH₃)₂. In some embodiments, R₆₀ is C(O)R wherein R is C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched alkoxy, phenyl, aryl or heteroaryl. In some embodiments, R₆₀ is S(O)₂R wherein R is C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched alkoxy, phenyl, aryl or heteroaryl. In some
 5 embodiments, R₆₀ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g.,
 10 cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

[0073] In some embodiments, R₈ of formula **I-IX** is CH₂. In other embodiments, R₈ is CH₂CH₂. In other embodiments, R₈ is CH₂CH₂CH₂. In some embodiments, R₈ is CH₂CH₂CH₂CH₂.
 15 [0074] In some embodiments, **p** of formula **I-IX** 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 some embodiments, **p** is between 1 and 5. In some embodiments, **p** is between 1 and 10.

[0075] In some embodiments, R₉ of formula **I-IX** is C≡C. In some embodiments, R₉ is C≡C-C≡C. In
 20 some embodiments, R₉ is CH=CH. In some embodiments, R₉ is CH=CH-CH=CH.

[0076] In some embodiments, **q** of formula **I-IX** 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.

[0077] In some embodiments, R₁₀ of formula **I-IX** is C₁-C₅ linear or branched alkyl. In other embodiments, R₁₀ is H. In other embodiments, R₁₀ is CH₃. In other embodiments, R₁₀ is CH₂CH₃. In
 25 other embodiments, R₁₀ is CH₂CH₂CH₃. In some embodiments, R₁₀ is isopropyl. In some embodiments, R₁₀ is butyl. In some embodiments, R₁₀ is isobutyl. In some embodiments, R₁₀ is t-butyl. In some embodiments, R₁₀ is cyclopropyl. In some embodiments, R₁₀ is pentyl. In some embodiments, R₁₀ is isopentyl. In some embodiments, R₁₀ is neopentyl. In some embodiments, R₁₀ is benzyl. In other embodiments, R₁₀ is R₈-O-R₁₀. In other embodiments, R₁₀ is CH₂CH₂-O-CH₃. In other embodiments,
 30 R₁₀ is CN. In other embodiments, R₁₀ is C(O)R. In other embodiments, R₁₀ is C(O)(OCH₃). In other embodiments, R₁₀ is S(O)₂R.

[0078] In some embodiments, R₁₁ of formula **I-IX** is C₁-C₅ linear or branched alkyl. In other embodiments, R₁₁ is H. In other embodiments, R₁₁ is CH₃. In other embodiments, R₁₁ is CH₂CH₃. In
 35 other embodiments, R₁₁ is CH₂CH₂CH₃. In some embodiments, R₁₁ is isopropyl. In some embodiments, R₁₁ is butyl. In some embodiments, R₁₁ is isobutyl. In some embodiments, R₁₁ is t-butyl. In some embodiments, R₁₁ is cyclopropyl. In some embodiments, R₁₁ is pentyl. In some embodiments, R₁₁ is isopentyl. In some embodiments, R₁₁ is neopentyl. In some embodiments, R₁₁ is benzyl. In other embodiments, R₁₁ is R₈-O-R₁₀. In other embodiments, R₁₁ is CH₂CH₂-O-CH₃. In other embodiments,

R₁₁ is CN. In other embodiments, R₁₁ is C(O)R. In other embodiments, R₁₁ is C(O)(OCH₃). In other embodiments, R₁₁ is S(O)₂R.

[0079] In some embodiments, **R**₁₀ and **R**₁₁ of formula **I-IX** are joined to form a substituted or unsubstituted C₃-C₈ heterocyclic ring. In other embodiments, **R**₁₀ and **R**₁₁ are joint to form a piperazine ring. In other embodiments, **R**₁₀ and **R**₁₁ are joint to form a piperidine ring. In other embodiments, **R**₁₀ and **R**₁₁ are joint to form a morpholine ring. In other embodiments, **R**₁₀ and **R**₁₁ are joint to form a pyrrolidine ring. In other embodiments, **R**₁₀ and **R**₁₁ are joint to form a methylpiperazine ring. In other embodiments, **R**₁₀ and **R**₁₁ are joint to form an azetidine ring. In some embodiments, each of R₁₀ and/or R₁₁ may be further substituted by at least one selected from: F, Cl, Br, I, OH, C₁-C₅ linear or branched alkyl (e.g. methyl, ethyl, propyl), C₁-C₅ linear or branched alkyl-OH (e.g., C(CH₃)₂CH₂-OH, CH₂CH₂-OH), C₂-C₅ linear or branched alkenyl (e.g., *E*- or *Z*-propylene), C₂-C₅ linear or branched, substituted or unsubstituted alkynyl (e.g., CH≡C-CH₃), OH, alkoxy, ester (e.g., OC(O)-CH₃), N(R)₂, CF₃, aryl, phenyl, R₈-aryl (e.g., CH₂CH₂-Ph), heteroaryl (e.g., imidazole) C₃-C₈ cycloalkyl (e.g., cyclohexyl), C₃-C₈ heterocyclic ring (e.g., pyrrolidine), halophenyl, (benzyloxy)phenyl, alkyl-hydrogen-phosphate (e.g., tBu-PO₄H), dihydrogen-phosphate (i.e., OP(O)(OH)₂), dialkylphosphate (e.g., OP(O)(OCH₃)₂), CN and NO₂; each is a separate embodiment according to this invention.

[0080] In some embodiments, **R** of formula **I-IX** is H. In some embodiments, **R** is not H. In other embodiments, **R** is C₁-C₅ linear or branched alkyl. In other embodiments, **R** is methyl. In other embodiments, **R** is ethyl. In other embodiments, **R** is C₁-C₅ linear or branched alkoxy. In other embodiments, **R** is methoxy. In other embodiments, **R** is phenyl. In other embodiments, **R** is aryl. In other embodiments, **R** is heteroaryl. In other embodiments, two gem **R** substituents are joint together to form a 5 or 6 membered heterocyclic ring.

[0081] In various embodiments, **n** of compound of formula **I-V** is 0. 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 0 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.

[0082] In various embodiments, **m** of compound of formula **I-V** 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.

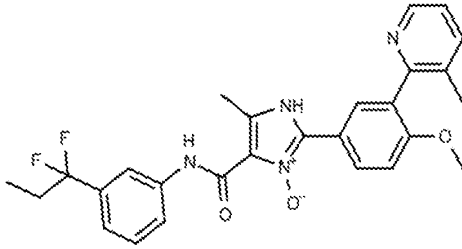
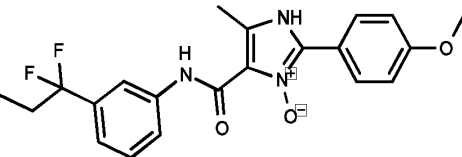
[0083] In various embodiments, **l** of compound of formula **I-V** is 0. In some embodiments, **l** is 0 or 1. In some embodiments, **l** is between 1 and 3. In some embodiments, **l** is between 1 and 4. In some embodiments, **l** is between 0 and 2. In some embodiments, **l** is between 0 and 3. In 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.

[0084] In various embodiments, **k** of compound of formula **I-V** 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.

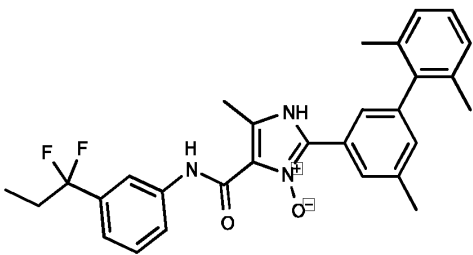
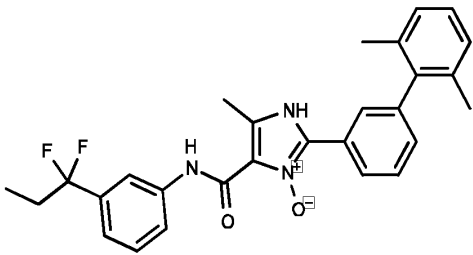
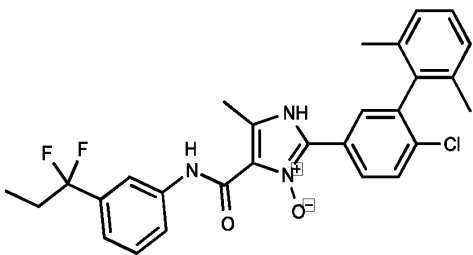
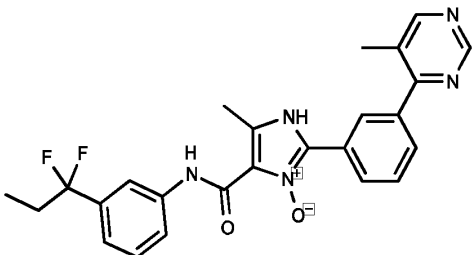
[0085] It is understood that for heterocyclic rings, **n**, **m**, **l** and/or **k** are limited to the number of available positions for substitution, i.e. to the number of CH or NH groups minus one. Accordingly, if A and/or B rings are, for example, furanyl, thiophenyl or pyrrolyl, **n**, **m**, **l** 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.

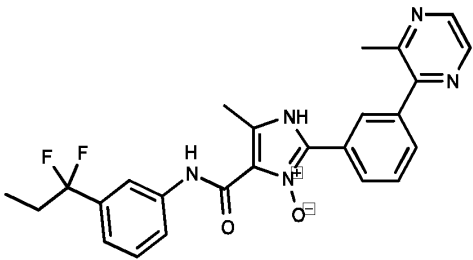
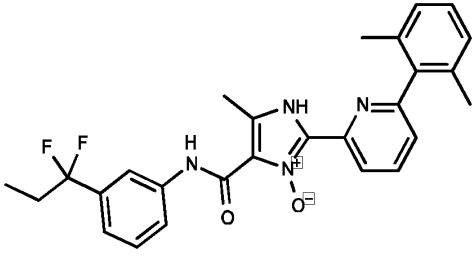
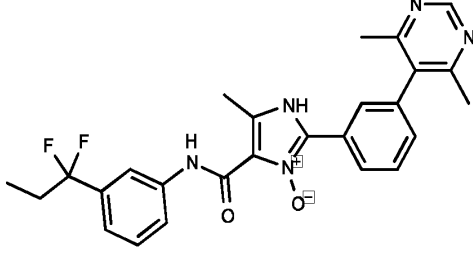
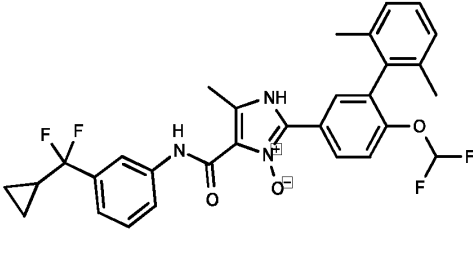
[0086] In various embodiments, this invention is directed to the compounds presented in Table 1, pharmaceutical compositions and/or method of use thereof:

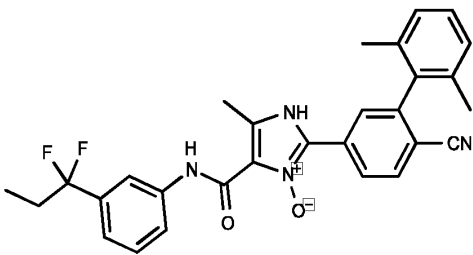
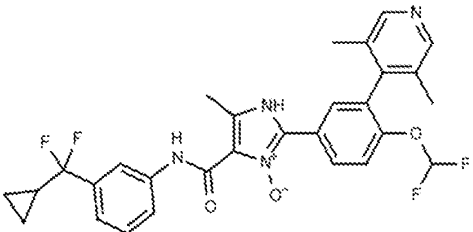
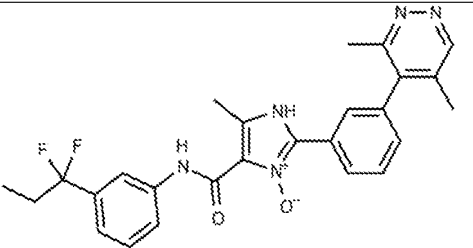
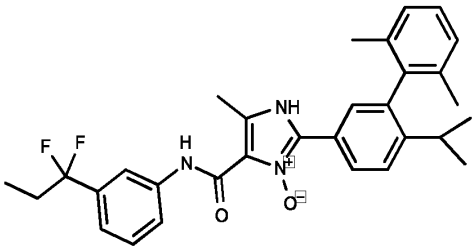
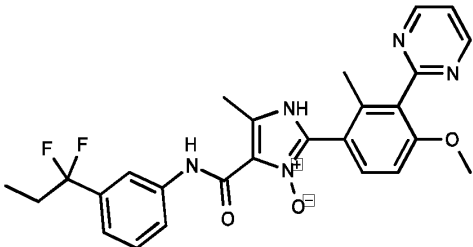
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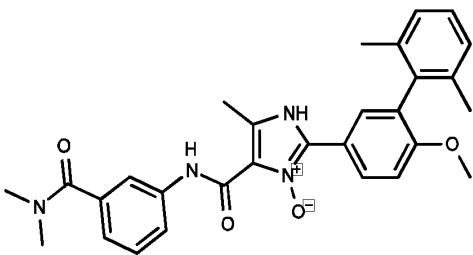
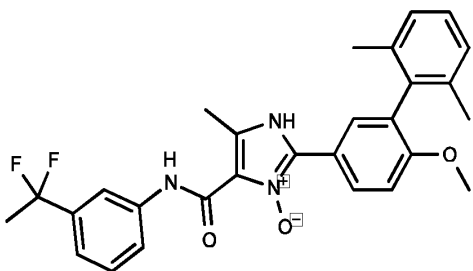
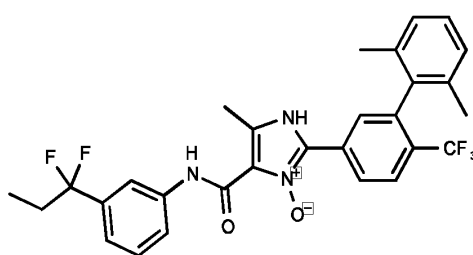
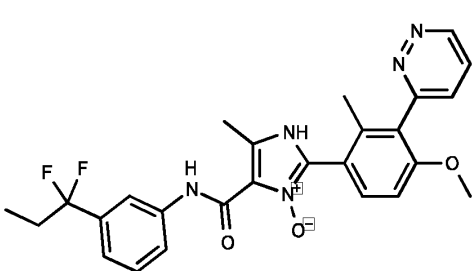
Compound Number	Compound Structure
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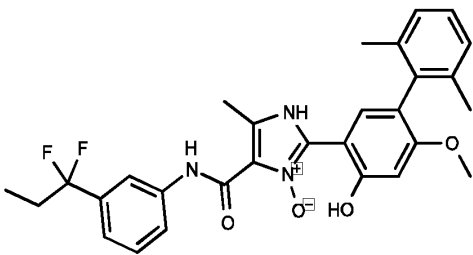
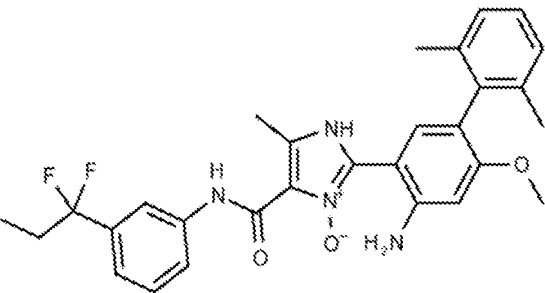
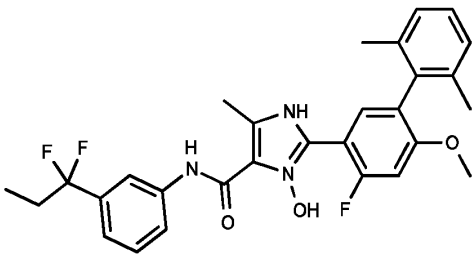
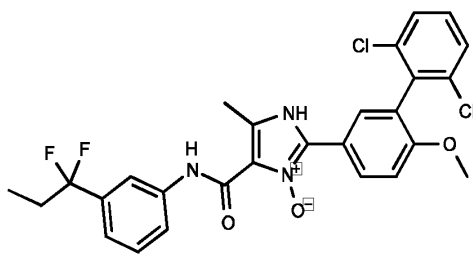
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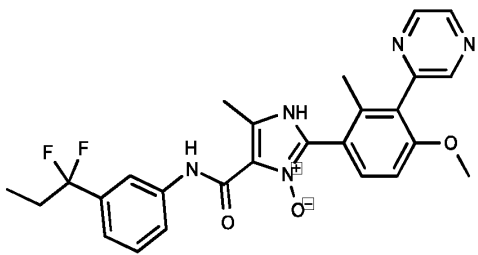
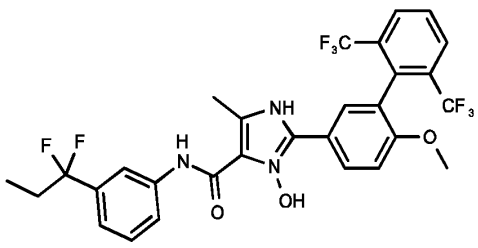
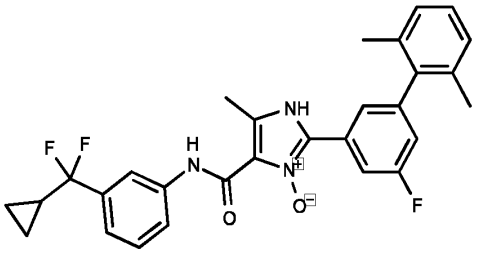
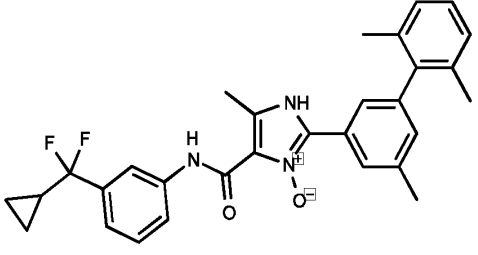
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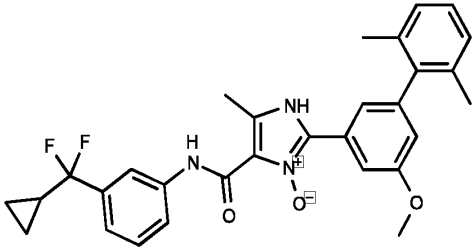
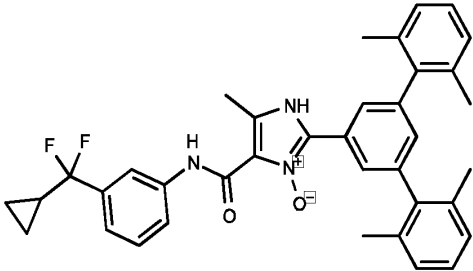
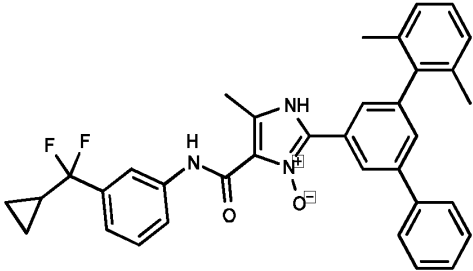
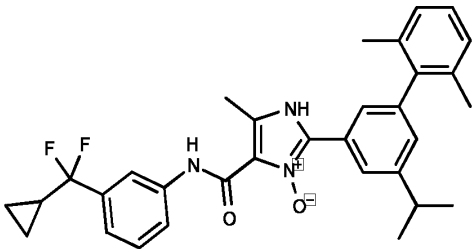
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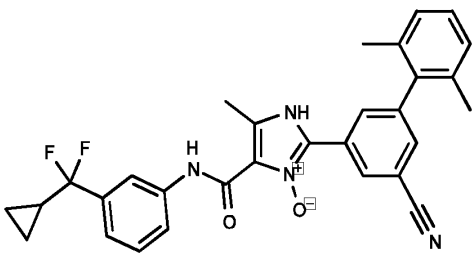
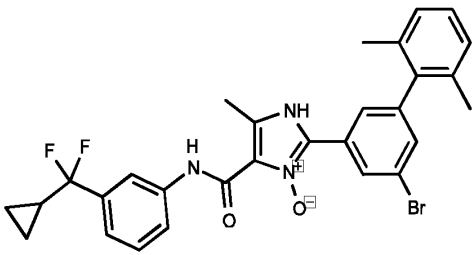
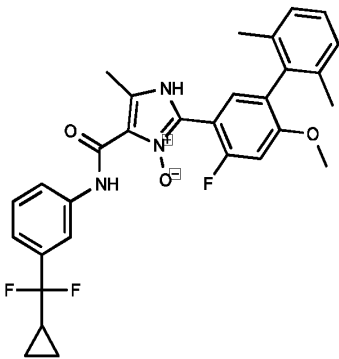
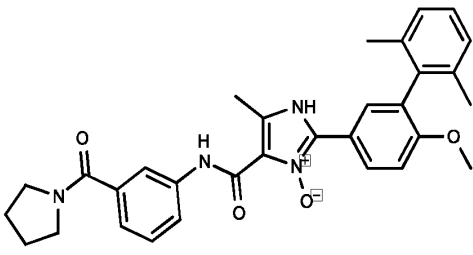
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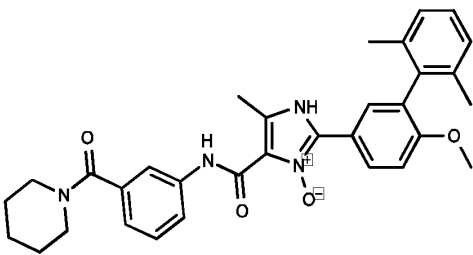
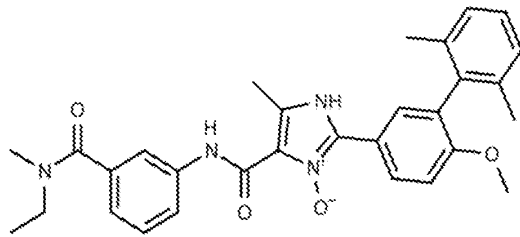
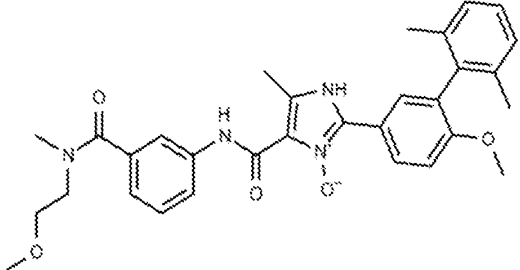
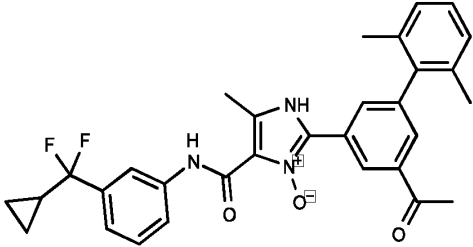
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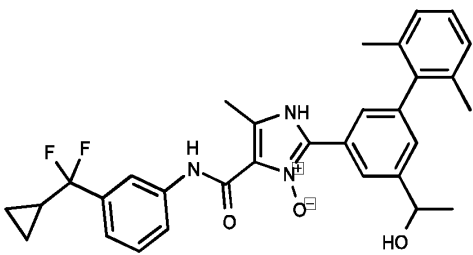
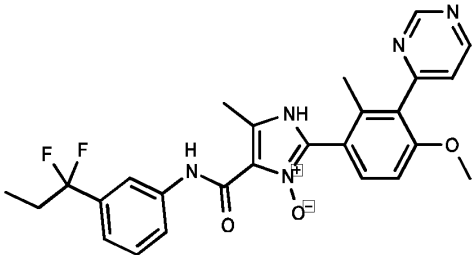
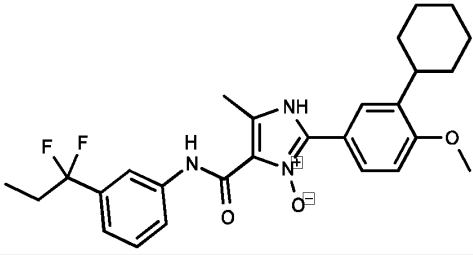
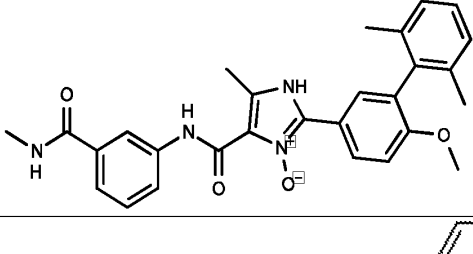
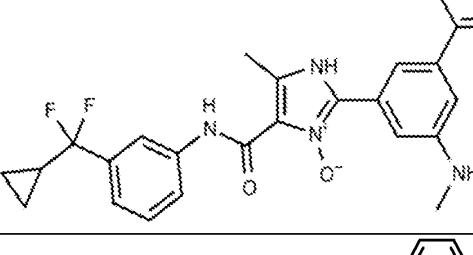
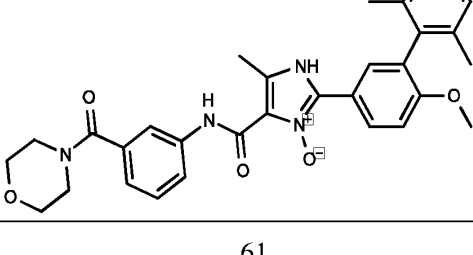
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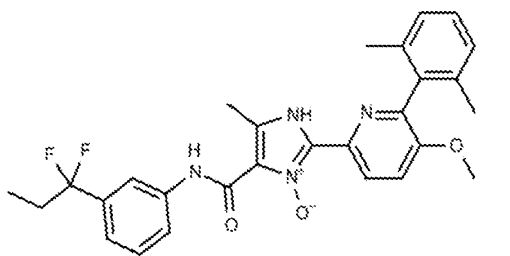
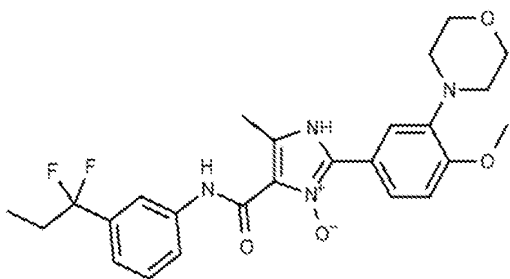
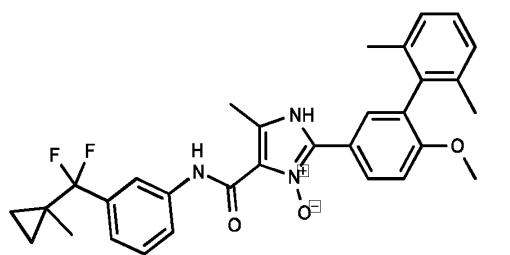
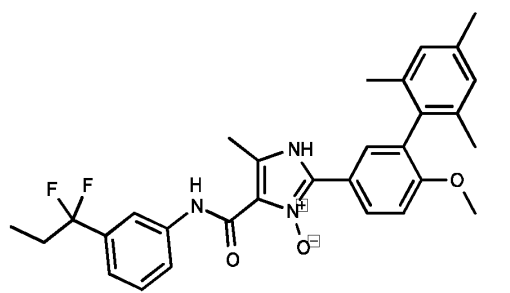
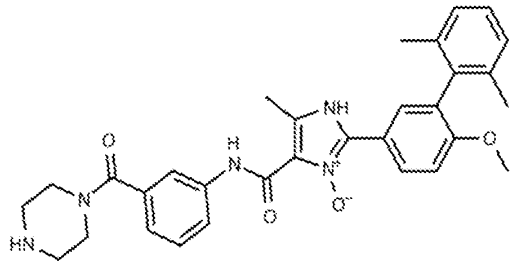
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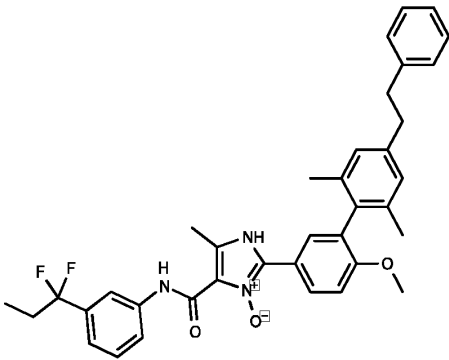
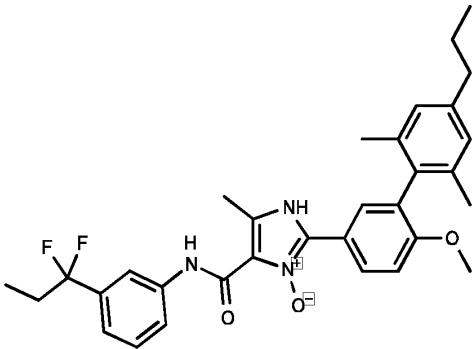
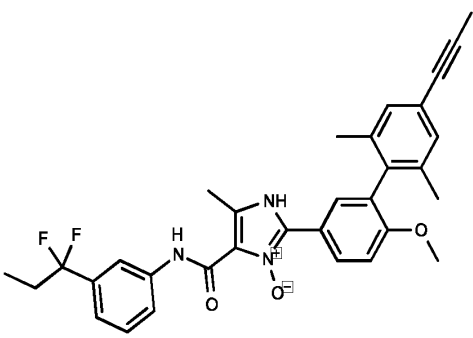
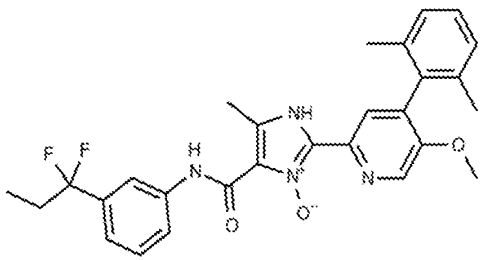
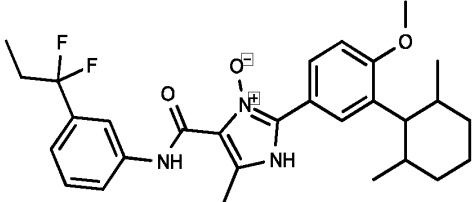
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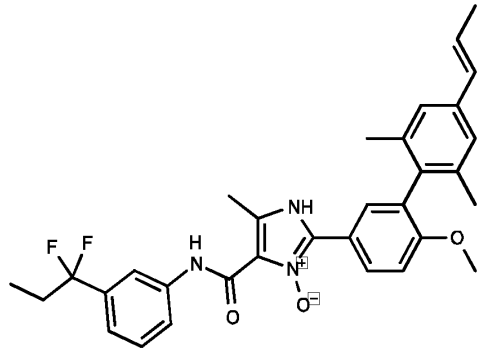
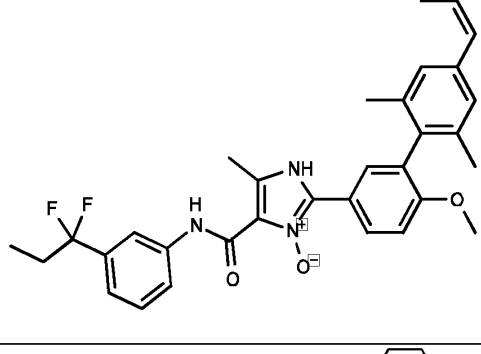
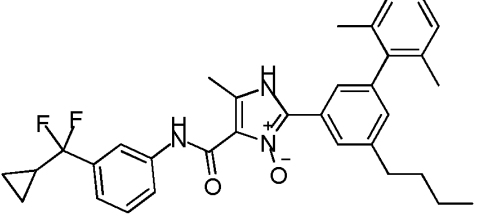
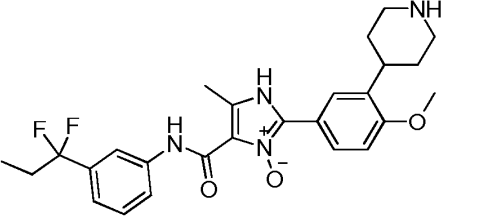
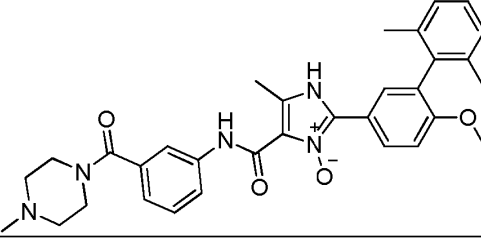
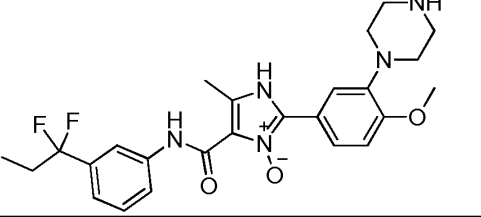
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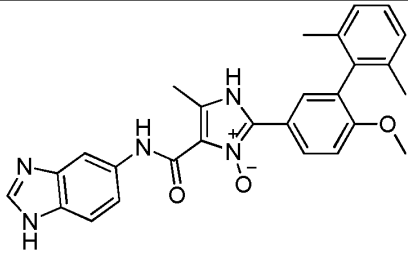
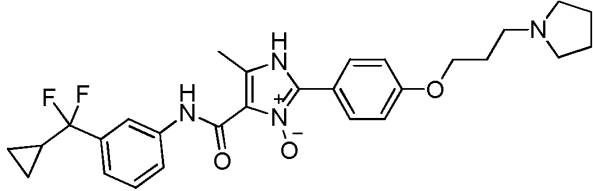
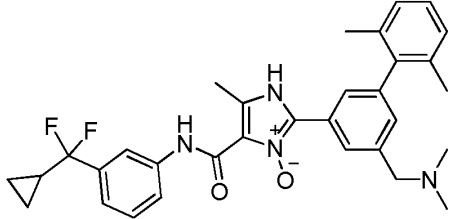
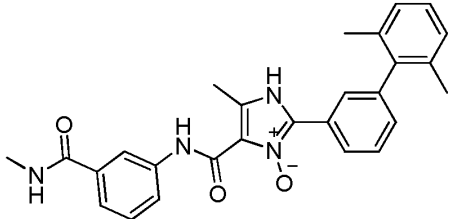
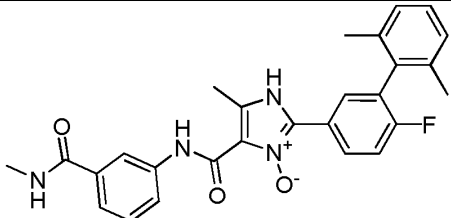
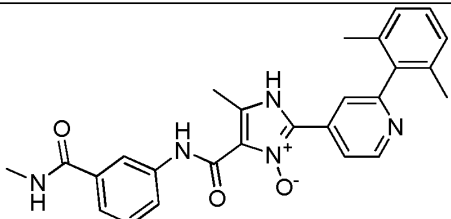
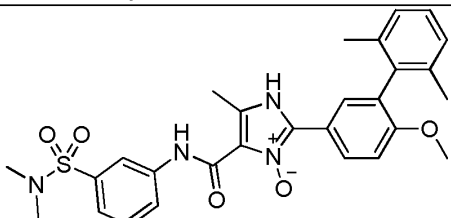
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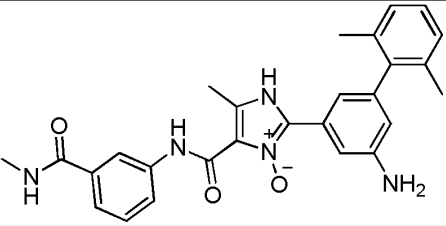
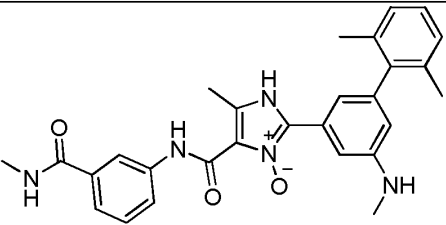
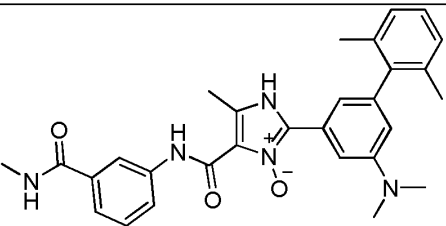
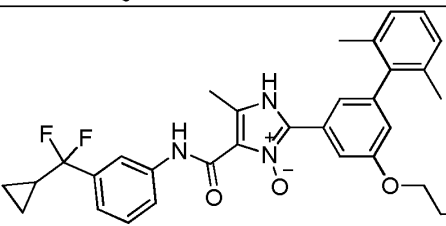
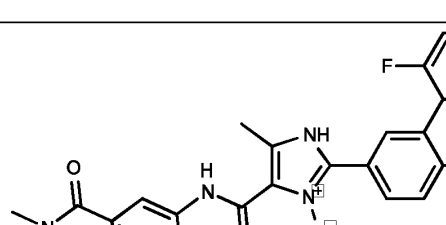
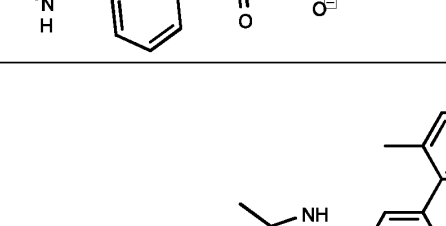
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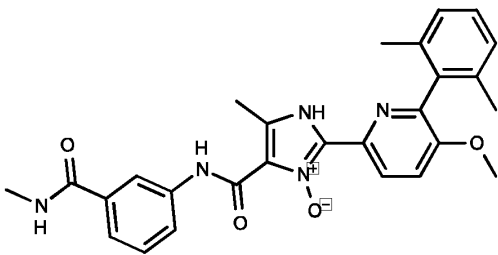
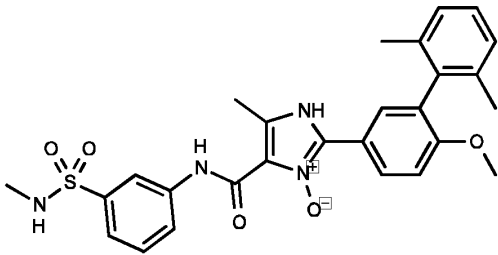
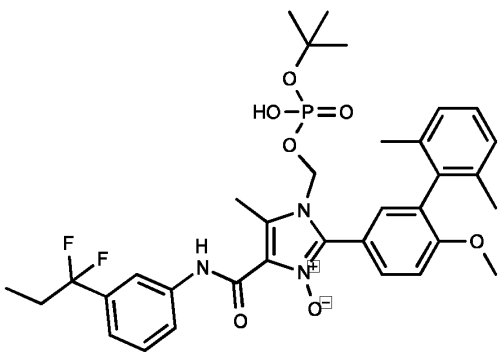
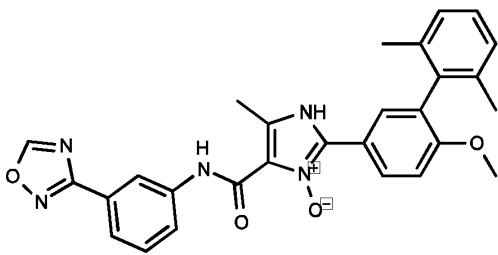
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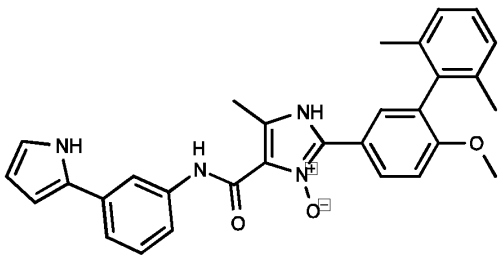
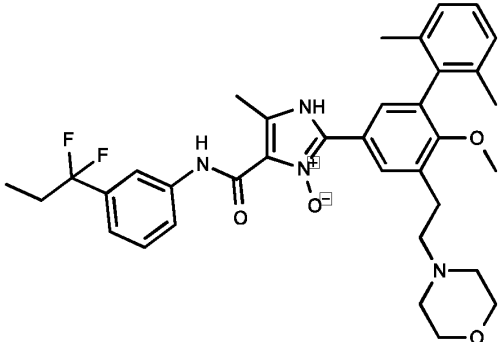
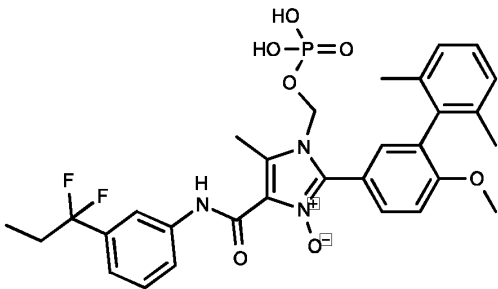
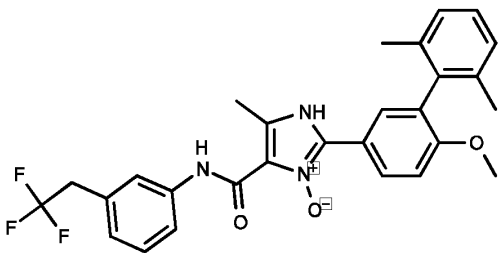
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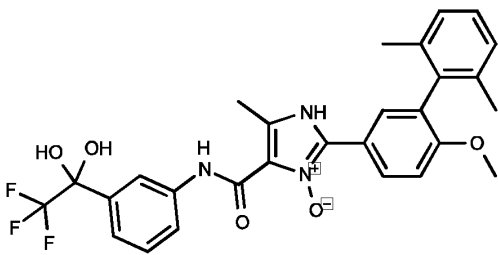
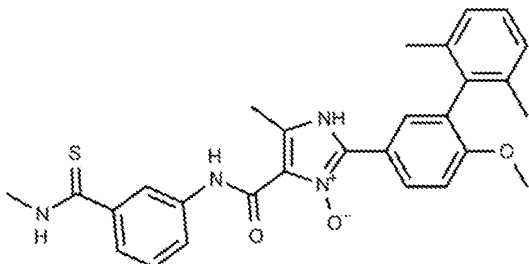
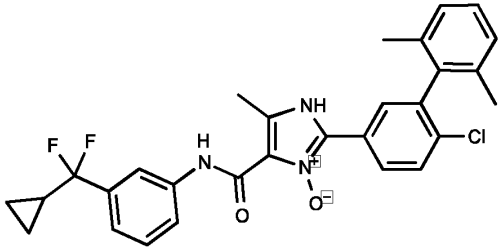
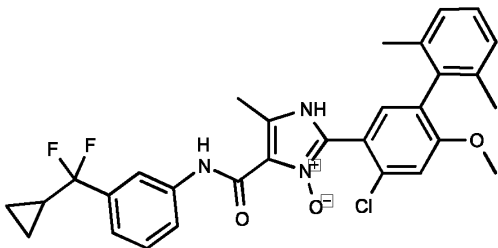
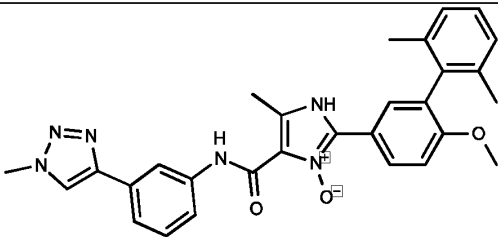
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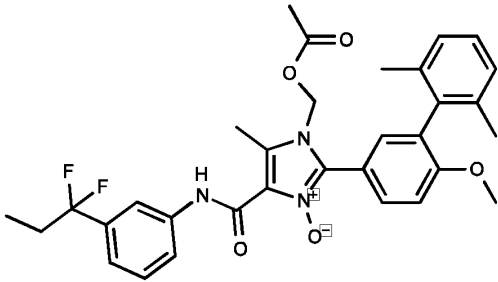
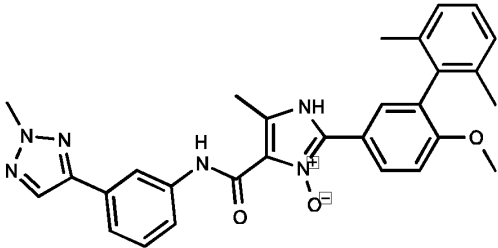
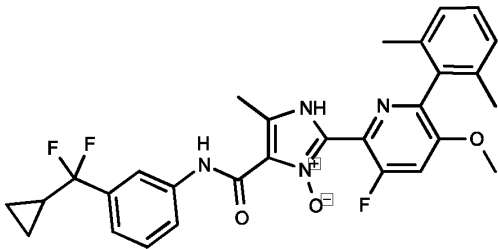
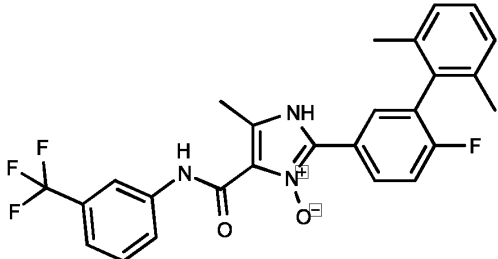
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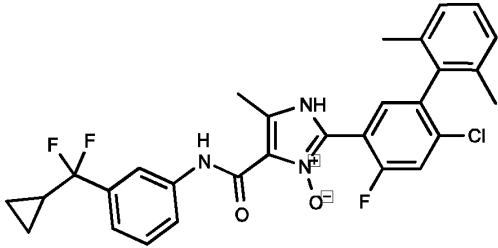
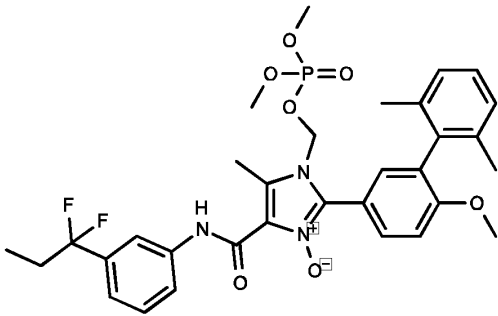
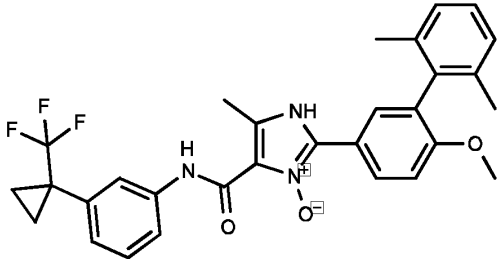
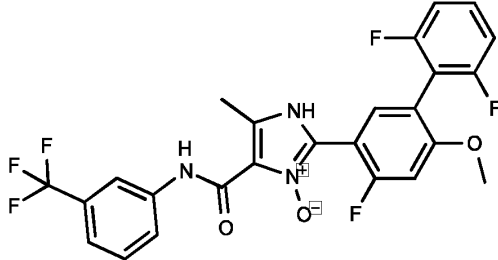
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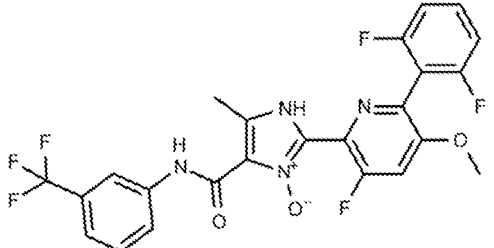
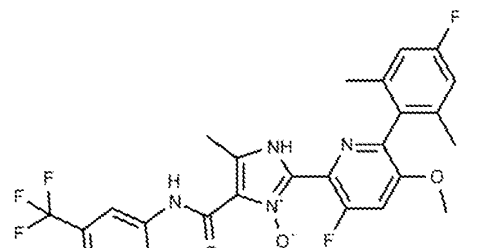
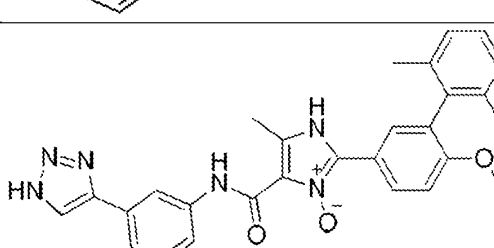
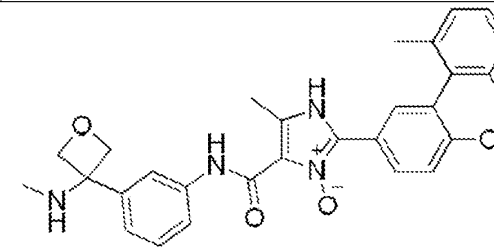
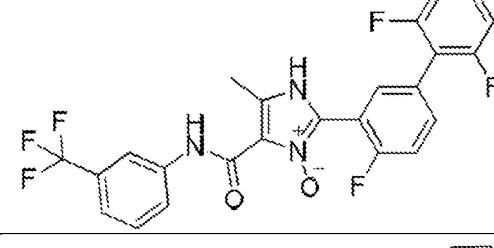
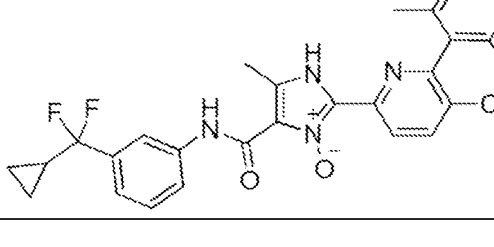
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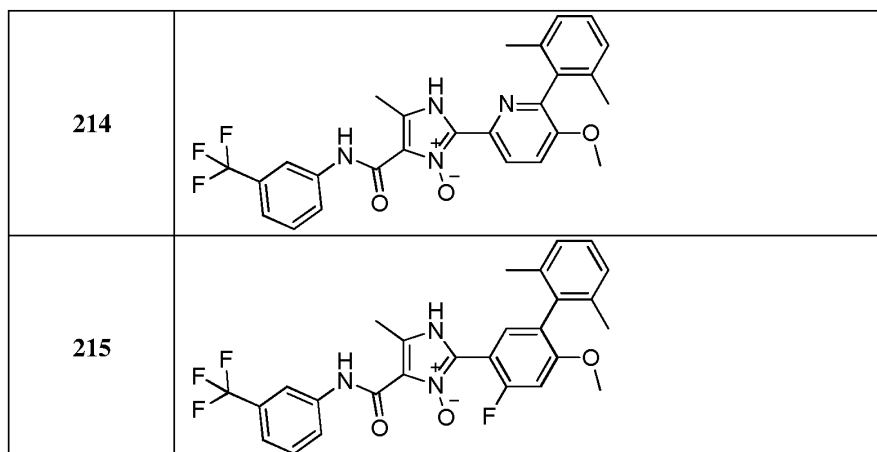
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[0087] It is well understood that in structures presented in this invention wherein the carbon atom has less than 4 bonds, H atoms are present to complete the valence of the carbon. It is well understood that in structures presented in this invention wherein the nitrogen atom has less than 3 bonds, H atoms are present to complete the valence of the nitrogen.

[0088] 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, reverse amide analog, prodrug, isotopic variant (deuterated analog), PROTAC, pharmaceutical product or any combination thereof. In some embodiments, the compounds are Acyl-CoA Synthetase Short-Chain Family Member 2 (ACSS2) inhibitors.

[0089] 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, oxadiazolyl, 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.

5 [0090] 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 C₁-C₅ carbons. In some embodiments, an alkyl includes C₁-C₆ carbons. In some embodiments, an alkyl includes C₁-C₈ carbons. In some embodiments, an alkyl includes C₁-C₁₀ carbons. In some embodiments, an alkyl is a C₁-C₁₂ carbons. In some embodiments, an alkyl is a C₁-C₂₀ carbons. In some embodiments, 10 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, CO₂H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C₁-C₅ linear or branched haloalkoxy, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, -CH₂CN, NH₂, NH-alkyl, N(alkyl)₂, -OC(O)CF₃, -OCH₂Ph, - 15 NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH₂ or any combination thereof.

[0091] 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, 20 arylmethyl, arylethyl, arylpropyl, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, methylamido, acetamido, propylamido, halomethylamido, haloethylamido, halopropylamido, methyl-urea, ethyl-urea, propyl-urea, 2, 3, or 4-CH₂-C₆H₄-Cl, C(OH)(CH₃)(Ph), etc.

[0092] As used herein, the term “alkenyl” can be any straight- or branched-chain alkenyl group containing up to about 30 carbons as defined hereinabove for the term “alkyl” and at least one carbon-carbon double bond. Accordingly, the term alkenyl as defined herein includes also alkadienes, alkatrienes, alkatetraenes, and so on. In some embodiments, the alkenyl group contains one carbon-carbon double bond. In some embodiments, the alkenyl group contains two, three, four, five, six, seven or eight carbon-carbon double bonds; each represents a separate embodiment according to this invention. Non limiting examples of alkenyl groups include: Ethenyl, Propenyl, Butenyl (i.e., 1-Butenyl, *trans*-2- 30 Butenyl, *cis*-2-Butenyl, and Isobutylene), Pentene (i.e., 1-Pentenyl, *cis*-2-Pentenyl, and *trans*-2-Pentenyl), Hexene (e.g., 1-Hexenyl, (*E*)-2-Hexenyl, (*Z*)-2-Hexenyl, (*E*)-3-Hexenyl, (*Z*)-3-Hexenyl, 2-Methyl-1-Pentene, etc.), which may all be substituted as defined herein above for the term “alkyl”.

[0093] As used herein, the term “alkynyl” can be any straight- or branched-chain alkynyl group containing up to about 30 carbons as defined hereinabove for the term “alkyl” and at least one carbon-carbon triple bond. Accordingly, the term alkynyl as defined herein includes also alkadiynes, alkatriynes, alkatetraynes, and so on. In some embodiments, the alkynyl group contains one carbon-carbon triple bond. In some embodiments, the alkynyl group contains two, three, four, five, six, seven or eight carbon-carbon triple bonds; each represents a separate embodiment according to this invention.

Non limiting examples of alkynyl groups include: acetylenyl, Propynyl, Butynyl (i.e., 1-Butynyl, 2-Butynyl, and Isobutylnyl), Pentyne (i.e., 1-Pentynyl, 2-Pentynyl), Hexyne (e.g., 1-Hexynyl, 2-Hexynyl, 3-Hexynyl, etc.), which may all be substituted as defined herein above for the term “alkyl”.

[0094] 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, C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl, C₁-C₅ linear or branched alkoxy, C₁-C₅ linear or branched haloalkoxy, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, CN, NO₂, -CH₂CN, NH₂, NH-alkyl, N(alkyl)₂, hydroxyl, -OC(O)CF₃, -OCH₂Ph, -NHCO-alkyl, COOH, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH₂ or any combination thereof.

[0095] 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.

[0096] 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, -NH₂.

[0097] 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 CF₃, CF₂CF₃, CF₂CH₃, CH₂CF₃, CF₂CH₂CH₃, CH₂CH₂CF₃, CF₂CH(CH₃)₂ and CF(CH₃)-CH(CH₃)₂.

[0098] A “haloalkenyl” group refers, in some embodiments, to an alkenyl group as defined above, which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I. The term “haloalkenyl” include but is not limited to fluoroalkenyl, i.e., to an alkenyl group bearing at least one fluorine atom, as well as their respective isomers if applicable (i.e., *E*, *Z* and/or *cis* and *trans*). Nonlimiting examples of haloalkenyl groups are CFCF₂, CF=CH-CH₃, CFCH₂-CHCF₂, CFCHCH₃, CHCHCF₃, and CF=C-(CH₃)₂ (both *E* and *Z* isomers where applicable).

[0099] A “halophenyl” group refers, in some embodiments, to a phenyl substituent 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.

[00100] 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 -CH₂-O-CH₃, -CH₂-O-CH(CH₃)₂, -CH₂-O-C(CH₃)₃, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-O-CH(CH₃)₂, -CH₂-CH₂-O-C(CH₃)₃.

[00101] 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, CO₂H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C₁-C₅ linear or branched haloalkoxy, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, -CH₂CN, NH₂, NH-alkyl, N(alkyl)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH₂ 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), cyclooctene (COE) etc.

[00102] 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, CO₂H, amino, alkylamino, dialkylamino, carboxyl, thio, thioalkyl, C₁-C₅ linear or branched haloalkoxy, CF₃, phenyl, halophenyl, (benzyloxy)phenyl, -CH₂CN, NH₂, NH-alkyl, N(alkyl)₂, -OC(O)CF₃, -OCH₂Ph, -NHCO-alkyl, -C(O)Ph, C(O)O-alkyl, C(O)H, -C(O)NH₂ 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.

[00103] 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.

[00104] In various embodiments, the term "isomer" includes, but is not limited to, stereoisomers, optical isomers, structural isomers, conformational isomers and analogs, and the like. In some embodiments, the isomer is an optical isomer. In some embodiments, the isomer is a stereoisomer.

[00105] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are included in this invention.

[00106] 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. The compounds according to this invention may further exist as stereoisomers which may be also optically-active isomers (e.g., enantiomers such as (*R*) or (*S*)), as enantiomerically enriched mixtures, racemic mixtures, or as single diastereomers, diastereomeric mixtures, or any other stereoisomers, including but not limited to: (*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*) stereoisomers. Some compounds may also exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or

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

[00107] 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).

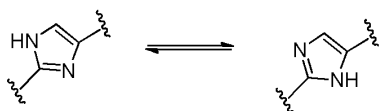
[00108] The compounds of the present invention can also be present in the form of a racemic mixture, containing substantially equivalent amounts of stereoisomers. In some embodiments, the compounds of the present invention can be prepared or otherwise isolated, using known procedures, to obtain a stereoisomer 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.

[00109] 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.

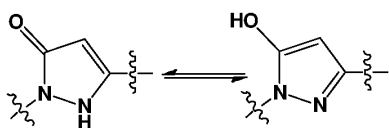
[00110] As used herein, when some chemical functional group (e.g. alkyl or aryl) is said to be "substituted", it is herein defined that one or more substitutions are possible.

[00111] 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:



[00112] 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, oxalic 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.

[00113] 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.

[00114] 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, glycolylarsanilates, glutarates, glutamate, heptanoates, hexanoates, hydroxymaleates, hydroxycarboxylic 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, nicotines, 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.

[00115] 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.

[00116] 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, picolines, piperazines, procain, tris(hydroxymethyl)methylamines, triethylamines, triethanolamines, trimethylamines, tromethamines and ureas.

[00117] 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.

10 *Pharmaceutical composition*

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] 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.

5 [00123] 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
10 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.

[00124] 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.

15 [00125] 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
20 dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[00126] 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
25 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.

30 [00127] 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
35 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.

- [00128] 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.
- 5 [00129] In various embodiments, the compounds of this invention are administered in combination with an anti-cancer agent. In various embodiments, the anti-cancer agent is a monoclonal antibody. In some embodiments, the monoclonal antibodies are used for diagnosis, monitoring, or treatment of cancer. In various embodiments, monoclonal antibodies react against specific antigens on cancer cells. In various
10 embodiments, the monoclonal antibody acts as a cancer cell receptor antagonist. In various embodiments, monoclonal antibodies enhance the patient's immune response. In various embodiments, monoclonal antibodies act against cell growth factors, thus blocking cancer cell growth. In various embodiments, anti-cancer monoclonal antibodies are conjugated or linked to anti-cancer drugs, radioisotopes, other biologic response modifiers, other toxins, or a combination thereof. In various
15 embodiments, anti-cancer monoclonal antibodies are conjugated or linked to a compound of this invention as described hereinabove.
- [00130] In various embodiments, the compounds of this invention are administered in combination with an agent treating an autoimmune disease.
- [00131] In various embodiments, the compounds of this invention are administered in combination with an agent treating an inflammatory condition .
- 20 [00132] In various embodiments, the compounds of this invention are administered in combination with an agent treating a neuropsychiatric disease.
- [00133] In various embodiments, the compounds of this invention are administered in combination with an agent treating a metabolic disorder.
- [00134] In various embodiments, the compounds of this invention are administered in combination with
25 an agent treating non-alcoholic steatohepatitis (NASH).
- [00135] In various embodiments, the compounds of this invention are administered in combination with an agent treating non alcoholic fatty liver disease (NAFLD).
- [00136] In various embodiments, the compounds of this invention are administered in combination with an agent treating alcoholic steatohepatitis (ASH).
- 30 [00137] In various embodiments, the compounds of this invention are administered in combination with an agent treating human cytomegalovirus (HCMV) infection.
- [00138] In various embodiments, the compounds of this invention are administered in combination with an anti-viral agent.
- [00139] In various embodiments, the compounds of this invention are administered in combination with
35 at least one of the following: chemotherapy, molecularly-targeted therapies, DNA damaging agents, hypoxia-inducing agents, or immunotherapy, each possibility represents a separate embodiment of this invention.

[00140] Yet another aspect of the present invention relates to a method of treating cancer that includes selecting a subject in need of treatment for cancer and administering to the subject a pharmaceutical composition comprising a compound according to the first aspect of the present invention and a pharmaceutically acceptable carrier under conditions effective to treat cancer.

5 [00141] 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 cancer cells or precancerous cells are present. Thus, administering can be accomplished in any manner effective for delivering the compounds or the pharmaceutical compositions to the cancer cells or precancerous cells. Exemplary modes of administration include, without limitation, administering the compounds or
10 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.

15 ***Biological Activity***

[00142] 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
20 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.

[00143] Acetate is an important source of acetyl-CoA in hypoxia. Inhibition of acetate metabolism may impair tumor growth. The nucleocytosolic acetyl-CoA synthetase enzyme, ACSS2, supplies a key source
25 of acetyl-CoA for tumors by capturing acetate as a carbon source. Despite exhibiting no gross deficits in growth or development, adult mice lacking ACSS2 exhibit a significant reduction in tumor burden in two different models of hepatocellular carcinoma. ACSS2 is expressed in a large proportion of human tumors, and its activity is responsible for the majority of cellular acetate uptake into both lipids and histones. Further, ACSS2 was identified in an unbiased functional genomic screen as a critical enzyme for the growth and
30 survival of breast and prostate cancer cells cultured in hypoxia and low serum. Indeed, high expression of ACSS2 is frequently found in invasive ductal carcinomas of the breast, triple-negative breast cancer, glioblastoma, ovarian cancer, pancreatic cancer and lung cancer, and often directly correlates with higher-grade tumours and poorer survival compared with tumours that have low ACSS2 expression. These observations may qualify ACSS2 as a targetable metabolic vulnerability of a wide spectrum of tumors.

35 [00144] Therefore, in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting cancer comprising administering a compound of this invention to a subject suffering from cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the cancer. In some

embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the cancer is early cancer. In some embodiments, the cancer is advanced cancer. In some embodiments, the cancer is invasive cancer. In some embodiments, the cancer is metastatic cancer. In some embodiments, the cancer is drug resistant cancer. In some embodiments, the cancer is selected from the list presented below:

Cancer, bladder (urothelial carcinoma)
Myelodysplasia
Cancer, breast (inflammatory)
Cancer, cervix
Cancer, endometrium
Cancer, esophagus
Cancer, head and neck (squamous cell carcinoma)
Cancer, kidney (renal cell carcinoma)
Cancer, kidney (renal cell carcinoma, clear cell)
Cancer, liver (hepatocellular carcinoma)
Cancer, lung (non-small cell) (NSCLC)
Cancer, metastatic (to brain)
Cancer, nasopharynx
Cancer, solid tumor
Cancer, stomach
Carcinoma, adrenocortical
Glioblastoma multiforme
Leukemia, acute myeloid
Leukemia, chronic lymphocytic
Lymphoma, Hodgkin's (classical)
Lymphoma, diffuse large B-cell
Lymphoma, primary central nervous system
Melanoma, malignant
Melanoma, uveal
Meningioma
Multiple myeloma
Cancer, breast

Cancer
Cancer, anus
Cancer, anus (squamous cell)
Cancer, biliary
Cancer, bladder, muscle invasive urothelial carcinoma
Cancer, breast metastatic
Cancer, colorectal
Cancer, colorectal metastatic
Cancer, fallopian tube
Cancer, gastroesophageal junction
Cancer, gastroesophageal junction (adenocarcinoma)
Cancer, larynx (squamous cell)
Cancer, lung (non-small cell) (NSCLC) (squamous cell carcinoma)
Cancer, lung (non-small cell) (NSCLC) metastatic
Cancer, lung (small cell) (SCLC)
Cancer, lung (small cell) (SCLC) (extensive)
Cancer, merkel cell
Cancer, mouth
Cancer, ovary
Cancer, ovary (epithelial)
Cancer, pancreas
Cancer, pancreas (adenocarcinoma)
Cancer, pancreas metastatic
Cancer, penis
Cancer, penis (squamous cell carcinoma)
Cancer, peritoneum
Cancer, prostate (castration-resistant)
Cancer, prostate (castration-resistant), metastatic
Cancer, rectum

Cancer, skin (basal cell carcinoma)
Cancer, skin (squamous cell carcinoma)
Cancer, small intestine (adenocarcinoma)
Cancer, testis
Cancer, thymus
Cancer, thyroid, anaplastic
Cholangiocarcinoma
Chordoma
Cutaneous T-cell lymphoma
Digestive-gastrointestinal cancer
Familial pheochromocytoma- paraganglioma
Glioma
HTLV-1-associated adult T-cell leukemia- lymphoma
Hematologic-blood cancer
Hepatitis C (HCV)
Infection, papillomaviral respiratory
Leiomyosarcoma, uterine
Leukemia, acute lymphocytic
Leukemia, chronic myeloid
Lymphoma, T-cell
Lymphoma, follicular
Lymphoma, primary mediastinal large B- cell
Lymphoma, testicular, diffuse large B-cell
Melanoma
Mesothelioma, malignant
Mesothelioma, pleural
Mycosis fungoides
Neuroendocrine cancer
Oral epithelial dysplasia
Sarcoma
Sepsis, severe
Sezary syndrome
Smoldering myeloma
Soft tissue sarcoma

T-cell lymphoma, nasal natural killer (NK) cell
T-cell lymphoma, peripheral

- [00145] In some embodiments, the cancer is selected from the list of: hepatocellular carcinoma, melanoma (e.g., BRAF mutant melanoma), glioblastoma, breast cancer, prostate cancer, liver cancer, brain cancer, Lewis lung carcinoma (LLC), colon carcinoma, pancreatic cancer, renal cell carcinoma, and mammary carcinoma. In some embodiments, the cancer is selected from the list of: melanoma, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, Hodgkin lymphoma, Merkel cell skin cancer (Merkel cell carcinoma), esophagus cancer; gastroesophageal junction cancer; liver cancer, (hepatocellular carcinoma); lung cancer, (small cell) (SCLC); stomach cancer; upper urinary tract cancer, (urothelial carcinoma); multiforme Glioblastoma; Multiple myeloma; anus cancer, (squamous cell); cervix cancer; endometrium cancer; nasopharynx cancer; ovary cancer; metastatic pancreas cancer; solid tumor cancer; adrenocortical Carcinoma; HTLV-1-associated adult T-cell leukemia-lymphoma; uterine Leiomyosarcoma; acute myeloid Leukemia; chronic lymphocytic Leukemia; diffuse large B-cell Lymphoma; follicular Lymphoma; uveal Melanoma; Meningioma; pleural Mesothelioma; Myelodysplasia; Soft tissue sarcoma; breast cancer; colon cancer; Cutaneous T-cell lymphoma; and peripheral T-cell lymphoma. In some embodiments, the cancer is selected from the list of: glioblastoma, melanoma, lymphoma, breast cancer, ovarian cancer, glioma, digestive system cancer, central nervous system cancer, hepatocellular cancer, hematological cancer, colon cancer or any combination thereof. 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.
- [00146] It has been shown that glucose-independent acetate metabolism promotes melanoma cell survival and tumor growth. Glucose-starved melanoma cells are highly dependent on acetate to sustain ATP levels, cell viability and proliferation. Conversely, depletion of ACSS1 or ACSS2 reduced melanoma tumor growth in mice. Collectively, this data demonstrates acetate metabolism as a liability in melanoma.
- [00147] Accordingly, in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting melanoma comprising administering a compound of this invention to a subject suffering from melanoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the melanoma. In some embodiments, the melanoma is early melanoma. In some embodiments, the melanoma is advanced melanoma. In some embodiments, the melanoma is invasive melanoma. In some embodiments, the melanoma is metastatic melanoma. In some embodiments, the melanoma is drug resistant melanoma. In some embodiments, the melanoma is BRAF mutant melanoma. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5.

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.

[00148] Acetyl-CoA synthetases that catalyse the conversion of acetate to acetyl-CoA have now been implicated in the growth of hepatocellular carcinoma, glioblastoma, breast cancer and prostate cancer.

5 [00149] Hepatocellular carcinoma (HCC) is a deadly form of liver cancer, and it is currently the second leading cause of cancer-related deaths worldwide (European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer, 2012). Despite a number of available treatment strategies, the survival rate for HCC patients is low. Considering its rising prevalence, more targeted and effective treatment strategies are highly desirable for HCC.

10 [00150] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting hepatocellular carcinoma (HCC) comprising administering a compound of this invention to a subject suffering from hepatocellular carcinoma (HCC) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the hepatocellular carcinoma (HCC). In some embodiments, the hepatocellular carcinoma (HCC) is early
15 hepatocellular carcinoma (HCC). In some embodiments, the hepatocellular carcinoma (HCC) is advanced hepatocellular carcinoma (HCC). In some embodiments, the hepatocellular carcinoma (HCC) is invasive hepatocellular carcinoma (HCC). In some embodiments, the hepatocellular carcinoma (HCC) is metastatic hepatocellular carcinoma (HCC). In some embodiments, the hepatocellular carcinoma (HCC) is drug resistant hepatocellular carcinoma (HCC). In some embodiments, the compound is an ACSS2 inhibitor. In
20 some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

25 [00151] ACSS2-mediated acetate metabolism contributes to lipid synthesis and aggressive growth in glioblastoma and breast cancer.

[00152] Nuclear ACSS2 is shown to activate HIF-2 α by acetylation and thus accelerate growth and metastasis of HIF2 α -driven cancers such as certain Renal Cell Carcinoma and Glioblastomas (Chen, R. et al. Coordinate regulation of stress signaling and epigenetic events by Acss2 and HIF-2 in cancer
30 cells, Plos One, 12 (12) 1-31, 2017).

[00153] Therefore, and in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting glioblastoma comprising administering a compound of this invention to a subject suffering from glioblastoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the glioblastoma. In
35 some embodiments, the glioblastoma is early glioblastoma. In some embodiments, the glioblastoma is advanced glioblastoma. In some embodiments, the glioblastoma is invasive glioblastoma. In some embodiments, the glioblastoma is metastatic glioblastoma. In some embodiments, the glioblastoma is drug resistant glioblastoma. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments,

the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00154] Therefore, and in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting Renal Cell Carcinoma comprising administering a compound of this invention to a subject suffering from Renal Cell Carcinoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the Renal Cell Carcinoma. In some embodiments, the Renal Cell Carcinoma is early Renal Cell Carcinoma. In some embodiments, the Renal Cell Carcinoma is advanced Renal Cell Carcinoma. In some embodiments, the Renal Cell Carcinoma is invasive Renal Cell Carcinoma. In some embodiments, the Renal Cell Carcinoma is metastatic Renal Cell Carcinoma. In some embodiments, the Renal Cell Carcinoma is drug resistant Renal Cell Carcinoma. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00155] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting breast cancer comprising administering a compound of this invention to a subject suffering from breast cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the breast cancer. In some embodiments, the breast cancer is early breast cancer. In some embodiments, the breast cancer is advanced breast cancer. In some embodiments, the breast cancer is invasive breast cancer. In some embodiments, the breast cancer is metastatic breast cancer. In some embodiments, the breast cancer is drug resistant breast cancer. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00156] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting prostate cancer comprising administering a compound of this invention to a subject suffering from prostate cancer under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the prostate cancer. In some embodiments, the prostate cancer is early prostate cancer. In some embodiments, the prostate cancer is advanced prostate cancer. In some embodiments, the prostate cancer is invasive prostate cancer. In some embodiments, the prostate cancer is metastatic prostate cancer. In some embodiments, the prostate cancer

is drug resistant prostate cancer. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. In some
5 embodiments, the compound is any one of the compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00157] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting liver cancer comprising administering a compound of this invention to a subject suffering from liver cancer under conditions effective to treat, suppress, reduce
10 the severity, reduce the risk of developing, or inhibit the liver cancer. In some embodiments, the liver cancer is early liver cancer. In some embodiments, the liver cancer is advanced liver cancer. In some embodiments, the liver cancer is invasive liver cancer. In some embodiments, the liver cancer is metastatic liver cancer. In some embodiments, the liver cancer is drug resistant liver cancer. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments,
15 the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00158] Nuclear ACSS2 is also shown to promote lysosomal biogenesis, autophagy and to promote brain tumorigenesis by affecting Histone H3 acetylation (Li, X *et al.*: Nucleus-Translocated ACSS2 Promotes Gene Transcription for Lysosomal Biogenesis and Autophagy, *Molecular Cell* 66, 1-14, **2017**).

[00159] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting brain cancer comprising administering a compound of this invention to a subject suffering from brain cancer under conditions effective to treat,
25 suppress, reduce the severity, reduce the risk of developing, or inhibit the brain cancer. In some embodiments, the brain cancer is early brain cancer. In some embodiments, the brain cancer is advanced brain cancer. In some embodiments, the brain cancer is invasive brain cancer. In some embodiments, the brain cancer is metastatic brain cancer. In some embodiments, the brain cancer is drug resistant brain cancer. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments,
30 the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00160] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting pancreatic cancer comprising administering a compound of this invention to a subject suffering from pancreatic cancer under conditions effective to treat,
35 suppress, reduce the severity, reduce the risk of developing, or inhibit the pancreatic cancer. In some embodiments, the pancreatic cancer is early pancreatic cancer. In some embodiments, the pancreatic cancer

is advanced pancreatic cancer. In some embodiments, the pancreatic cancer is invasive pancreatic cancer. In some embodiments, the pancreatic cancer is metastatic pancreatic cancer. In some embodiments, the pancreatic cancer is drug resistant pancreatic cancer. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00161] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting Lewis lung carcinoma (LLC) comprising administering a compound of this invention to a subject suffering from Lewis lung carcinoma (LLC) under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the Lewis lung carcinoma (LLC). In some embodiments, the Lewis lung carcinoma (LLC) is early Lewis lung carcinoma (LLC). In some embodiments, the Lewis lung carcinoma (LLC) is advanced Lewis lung carcinoma (LLC). In some embodiments, the Lewis lung carcinoma (LLC) is invasive Lewis lung carcinoma (LLC). In some embodiments, the Lewis lung carcinoma (LLC) is metastatic Lewis lung carcinoma (LLC). In some embodiments, the Lewis lung carcinoma (LLC) is drug resistant Lewis lung carcinoma (LLC). In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00162] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting colon carcinoma comprising administering a compound of this invention to a subject suffering from colon carcinoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the colon carcinoma. In some embodiments, the colon carcinoma is early colon carcinoma. In some embodiments, the colon carcinoma is advanced colon carcinoma. In some embodiments, the colon carcinoma is invasive colon carcinoma. In some embodiments, the colon carcinoma is metastatic colon carcinoma. In some embodiments, the colon carcinoma is drug resistant colon carcinoma. In some embodiments, the compound is a 'program cell death receptor 1' (PD-1) modulator. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00163] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting mammary carcinoma comprising administering a compound of this invention to a subject suffering from mammary carcinoma under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the mammary carcinoma. In some embodiments, the mammary carcinoma is early mammary carcinoma. In some embodiments, the mammary carcinoma is advanced mammary carcinoma. In some embodiments, the mammary carcinoma is invasive mammary carcinoma. In some embodiments, the mammary carcinoma is metastatic mammary carcinoma. In some embodiments, the mammary carcinoma is drug resistant mammary carcinoma. In some embodiments, the compound is an ACSS2 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.

[00164] In various embodiments, this invention is directed to a method of suppressing, reducing or inhibiting tumour growth in a subject, comprising administering a compound according to this invention, to a subject suffering from a proliferative disorder (e.g., cancer) under conditions effective to suppress, reduce or inhibit said tumour growth in said subject. In some embodiments, the tumor growth is enhanced by increased acetate uptake by cancer cells. In some embodiments, the increase in acetate uptake is mediated by ACSS2. In some embodiments, the cancer cells are under hypoxic stress. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. In some embodiments, the tumor growth is suppressed due to suppression of lipid synthesis (e.g., fatty acid) induced by ACSS2 mediated acetate metabolism to acetyl-CoA. In some embodiments, the tumor growth is suppressed due to suppression of the regulation of histones acetylation and function induced by ACSS2 mediated acetate metabolism to acetyl-CoA. In some embodiments, the synthesis is suppressed under hypoxia (hypoxic stress). 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.

[00165] In various embodiments, this invention is directed to a method of suppressing, reducing or inhibiting lipid synthesis and/or regulating histones acetylation and function in a cell, comprising contacting a compound of this invention, with a cell under conditions effective to suppress, reduce or inhibit lipid synthesis and/or regulating histones acetylation and function in said cell. In various embodiments, the method is carried out *in vitro*. In various embodiments, the method is carried out *in vivo*. In various embodiments, the lipid synthesis is induced by ACSS2 mediated acetate metabolism to acetyl-CoA. In various embodiments, regulating histones acetylation and function is induced by ACSS2 mediated acetate metabolism to acetyl-CoA. In various embodiments, the cell is cancer cell. In various embodiments, the lipid is fatty acid. In various embodiments, the acetate metabolism to acetyl-CoA is carried out under hypoxia (i.e., hypoxic stress). In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some

embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00166] In various embodiments, this invention is directed to a method of suppressing, reducing or inhibiting fatty-acid accumulation in the liver, comprising administering a compound of this invention to a subject in need thereof, under conditions effective to suppress, reduce or inhibit fatty-acid accumulation in the liver of said subject. In various embodiments, the fatty-acid accumulation is induced by ACSS2 mediated acetate metabolism to acetyl-CoA. In various embodiments, the subject suffers from a fatty liver condition. In various embodiments, the acetate metabolism to acetyl-CoA in the liver is carried out under hypoxia (i.e., hypoxic stress). In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00167] In various embodiments, this invention is directed to a method of binding an ACSS2 inhibitor compound to an ACSS2 enzyme, comprising the step of contacting an ACSS2 enzyme with an ACSS2 inhibitor compound of this invention, in an amount effective to bind the ACSS2 inhibitor compound to the ACSS2 enzyme. In some embodiments, the method is carried out *in vitro*. In another embodiment, the method is carried out *in vivo*. 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.

[00168] In various embodiments, this invention is directed to a method of suppressing, reducing or inhibiting acetyl-CoA synthesis from acetate in a cell, comprising contacting a compound according to this invention with a cell, under conditions effective to suppress, reduce or inhibit acetyl-CoA synthesis from acetate in said cell. In some embodiments, the cell is a cancer cell. In some embodiments, the method is carried out *in vitro*. In another embodiment, the method is carried out *in vivo*. In some embodiments, the synthesis is mediated by ACSS2. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. In some embodiments, the cell is under hypoxic stress. 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.

[00169] In various embodiments, this invention is directed to a method of suppressing, reducing or inhibiting acetate metabolism in a cancer cell, comprising contacting a compound according to this invention with a cancer cell, under conditions effective to suppress, reduce or inhibit acetate metabolism in said cell. In some embodiments, the acetate metabolism is mediated by ACSS2. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to

both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. In some embodiments, the cancer cell is under hypoxic stress. 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.

- 5 [00170] In various embodiments, this invention provides methods for treating, suppressing, reducing the severity, reducing the risk, or inhibiting metastatic cancer comprising the step of administering to said subject a compound of this invention and/or an isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, polymorph, or crystal of said compound, or any combination
- 10 thereof. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is hepatocellular carcinoma. In some
- 15 embodiments, the cancer is glioblastoma. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is liver cancer. In some embodiments, the cancer is brain cancer. In some embodiments, the cancer is Lewis lung carcinoma. In some embodiments, the cancer is colon carcinoma. In some embodiments, the cancer is mammary carcinoma. In some embodiments, the cancer is pancreatic cancer.
- 20 [00171] In various embodiments, this invention provides methods for increasing the survival of a subject suffering from metastatic cancer comprising the step of administering to said subject a compound of this invention and/or an isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, polymorph, or crystal of said compound, or any combination thereof. In some embodiments,
- 25 the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is hepatocellular carcinoma. In some embodiments, the cancer is glioblastoma.
- 30 In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is liver cancer. In some embodiments, the cancer is brain cancer. In some embodiments, the cancer is Lewis lung carcinoma. In some embodiments, the cancer is colon carcinoma. In some embodiments, the cancer is mammary carcinoma. In some embodiments, the cancer is pancreatic cancer.
- 35 [00172] In various embodiments, this invention provides methods for treating, suppressing, reducing the severity, reducing the risk, or inhibiting advanced cancer comprising the step of administering to said subject a compound of this invention and/or an isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant

(e.g., deuterated analog), PROTAC, polymorph, or crystal of said compound, or any combination thereof. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is hepatocellular carcinoma. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is liver cancer. In some embodiments, the cancer is brain cancer. In some embodiments, the cancer is Lewis lung carcinoma. In some embodiments, the cancer is colon carcinoma. In some embodiments, the cancer is mammary carcinoma. In some embodiments, the cancer is pancreatic cancer.

[00173] In various embodiments, this invention provides methods for increasing the survival of a subject suffering from advanced cancer comprising the step of administering to said subject a compound of this invention and/or an isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, tautomer, hydrate, *N*-oxide, reverse amide analog, prodrug, isotopic variant (e.g., deuterated analog), PROTAC, polymorph, or crystal of said compound, or any combination thereof. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is hepatocellular carcinoma. In some embodiments, the cancer is glioblastoma. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is liver cancer. In some embodiments, the cancer is brain cancer. In some embodiments, the cancer is Lewis lung carcinoma. In some embodiments, the cancer is colon carcinoma. In some embodiments, the cancer is mammary carcinoma. In some embodiments, the cancer is pancreatic cancer.

[00174] The compounds of the present invention are useful in the treatment, reducing the severity, reducing the risk, or inhibition of cancer, metastatic cancer, advanced cancer, drug resistant cancer, and various forms of cancer. In a preferred embodiment the cancer is hepatocellular carcinoma, melanoma (e.g., BRAF mutant melanoma), glioblastoma, breast cancer, prostate cancer, liver cancer, brain cancer, pancreatic cancer, Lewis lung carcinoma (LLC), colon carcinoma, renal cell carcinoma, and/or mammary carcinoma; each represents a separate embodiment according to this invention. Based upon their believed mode of action, it is believed that other forms of cancer will likewise be treatable or preventable upon administration of the compounds or compositions of the present invention to a patient. Preferred compounds of the present invention are selectively disruptive to cancer cells, causing ablation of cancer cells but preferably not normal cells. Significantly, harm to normal cells is minimized because the cancer cells are susceptible to disruption at much lower concentrations of the compounds of the present invention.

- [00175] In various embodiments, other types of cancers that may be treatable with the ACSS2 inhibitors according to this invention include: adrenocortical carcinoma, anal cancer, bladder cancer, brain tumor, brain stem tumor, breast cancer, glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal, pineal tumors, hypothalamic glioma, carcinoid
- 5 tumor, carcinoma, cervical cancer, colon cancer, central nervous system (CNS) cancer, endometrial cancer, esophageal cancer, extrahepatic bile duct cancer, Ewing's family of tumors (Pnet), extracranial germ cell tumor, eye cancer, intraocular melanoma, gallbladder cancer, gastric cancer, germ cell tumor, extragonadal, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma, laryngeal cancer, leukemia, acute lymphoblastic, leukemia, oral cavity cancer, liver cancer, lung cancer,
- 10 non-small cell lung cancer, small cell, lymphoma, AIDS-related lymphoma, central nervous system (primary), lymphoma, cutaneous T-cell, lymphoma, Hodgkin's disease, non-Hodgkin's disease, malignant mesothelioma, melanoma, Merkel cell carcinoma, metastatic squamous carcinoma, multiple myeloma, plasma cell neoplasms, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, osteosarcoma, ovarian cancer, ovarian
- 15 epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, exocrine, pancreatic cancer, islet cell carcinoma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pheochromocytoma cancer, pituitary cancer, plasma cell neoplasm, prostate cancer, rhabdomyosarcoma, rectal cancer, renal cancer, renal cell cancer, salivary gland cancer, Sezary syndrome, skin cancer, cutaneous T-cell lymphoma, skin cancer, Kaposi's sarcoma, skin cancer, melanoma, small
- 20 intestine cancer, soft tissue sarcoma, soft tissue sarcoma, testicular cancer, thymoma, malignant, thyroid cancer, urethral cancer, uterine cancer, sarcoma, unusual cancer of childhood, vaginal cancer, vulvar cancer, Wilms' tumor, hepatocellular cancer, hematological cancer or any combination thereof. In some embodiments the cancer is invasive. In some embodiments the cancer is metastatic cancer. In some embodiments the cancer is advanced cancer. In some embodiments the cancer is drug resistant cancer.
- 25 [00176] In various embodiments "metastatic cancer" refers to a cancer that spread (metastasized) from its original site to another area of the body. Virtually all cancers have the potential to spread. Whether metastases develop depends on the complex interaction of many tumor cell factors, including the type of cancer, the degree of maturity (differentiation) of the tumor cells, the location and how long the cancer has been present, as well as other incompletely understood factors. Metastases spread in three ways - by local
- 30 extension from the tumor to the surrounding tissues, through the bloodstream to distant sites or through the lymphatic system to neighboring or distant lymph nodes. Each kind of cancer may have a typical route of spread. The tumor is called by the primary site (ex. breast cancer that has spread to the brain is called metastatic breast cancer to the brain).
- [00177] In various embodiments "drug-resistant cancer" refers to cancer cells that acquire resistance to
- 35 chemotherapy. Cancer cells can acquire resistance to chemotherapy by a range of mechanisms, including the mutation or overexpression of the drug target, inactivation of the drug, or elimination of the drug from the cell. Tumors that recur after an initial response to chemotherapy may be resistant to multiple drugs (they are multidrug resistant). In the conventional view of drug resistance, one or several cells in

the tumor population acquire genetic changes that confer drug resistance. Accordingly, the reasons for drug resistance, *inter alia*, are: a) some of the cells that are not killed by the chemotherapy mutate (change) and become resistant to the drug. Once they multiply, there may be more resistant cells than cells that are sensitive to the chemotherapy; b) Gene amplification. A cancer cell may produce hundreds of copies of a particular gene. This gene triggers an overproduction of protein that renders the anticancer drug ineffective; c) cancer cells may pump the drug out of the cell as fast as it is going in using a molecule called p-glycoprotein; d) cancer cells may stop taking in the drugs because the protein that transports the drug across the cell wall stops working; e) the cancer cells may learn how to repair the DNA breaks caused by some anti-cancer drugs; f) cancer cells may develop a mechanism that inactivates the drug. One major contributor to multidrug resistance is overexpression of P-glycoprotein (P-gp). This protein is a clinically important transporter protein belonging to the ATP-binding cassette family of cell membrane transporters. It can pump substrates including anticancer drugs out of tumor cells through an ATP-dependent mechanism; g) Cells and tumors with activating RAS mutations are relatively resistant to most anti-cancer agents. Thus, the resistance to anticancer agents used in chemotherapy is the main cause of treatment failure in malignant disorders, provoking tumors to become resistant. Drug resistance is the major cause of cancer chemotherapy failure.

[00178] In various embodiments “resistant cancer” refers to drug-resistant cancer as described herein above. In some embodiments “resistant cancer” refers to cancer cells that acquire resistance to any treatment such as chemotherapy, radiotherapy or biological therapy.

[00179] In various embodiments, this invention is directed to treating, suppressing, reducing the severity, reducing the risk, or inhibiting cancer in a subject, wherein the subject has been previously treated with chemotherapy, radiotherapy or biological therapy.

[00180] In various embodiments “Chemotherapy” refers to chemical treatment for cancer such as drugs that kill cancer cells directly. Such drugs are referred as “anti-cancer” drugs or “antineoplastics.” Today’s therapy uses more than 100 drugs to treat cancer. To cure a specific cancer. Chemotherapy is used to control tumor growth when cure is not possible; to shrink tumors before surgery or radiation therapy; to relieve symptoms (such as pain); and to destroy microscopic cancer cells that may be present after the known tumor is removed by surgery (called adjuvant therapy). Adjuvant therapy is given to prevent a possible cancer reoccurrence.

[00181] In various embodiments, “Radiotherapy” (also referred herein as “Radiation therapy”) refers to high energy x-rays and similar rays (such as electrons) to treat disease. Many people with cancer will have radiotherapy as part of their treatment. This can be given either as external radiotherapy from outside the body using x-rays or from within the body as internal radiotherapy. Radiotherapy works by destroying the cancer cells in the treated area. Although normal cells can also be damaged by the radiotherapy, they can usually repair themselves. Radiotherapy treatment can cure some cancers and can also reduce the chance of a cancer coming back after surgery. It may be used to reduce cancer symptoms.

[00182] In various embodiments “Biological therapy” refers to substances that occur naturally in the body to destroy cancer cells. There are several types of treatment including: monoclonal antibodies,

cancer growth inhibitors, vaccines and gene therapy. Biological therapy is also known as immunotherapy.

[00183] When the compounds or pharmaceutical compositions of the present invention are administered to treat, suppress, reduce the severity, reduce the risk, or inhibit a cancerous condition, the pharmaceutical composition can also contain, or can be administered in conjunction with, other therapeutic agents or treatment regimen presently known or hereafter developed for the treatment of various types of cancer. Examples of other therapeutic agents or treatment regimen include, without limitation, radiation therapy, immunotherapy, chemotherapy, surgical intervention, and combinations thereof.

[00184] It is this kind of metabolic plasticity — the ability to exploit and survive on a variety of nutritional sources — that confers resistance to many of the current cancer metabolism drugs as monotherapies. Interestingly, ACSS2 is highly expressed in many cancer tissues, and its upregulation by hypoxia and low nutrient availability indicates that it is an important enzyme for coping with the typical stresses within the tumour microenvironment and, as such, a potential Achilles heel. Moreover, highly stressed regions of tumours have been shown to select for apoptotic resistance and promote aggressive behaviour, treatment resistance and relapse. In this way, the combination of ACSS2 inhibitors with a therapy that specifically targets well-oxygenated regions of tumours (for example, radiotherapy) could prove to be an effective regimen.

[00185] Accordingly, and in various embodiments, the compound according to this invention, is administered in combination with an anti-cancer therapy. Examples of such therapies include but are not limited to: chemotherapy, immunotherapy, radiotherapy, biological therapy, surgical intervention, and combinations thereof. In some embodiments, the compound according to this invention is administered in combination with a therapy that specifically targets well-oxygenated regions of tumours. In some embodiments, the compound according to this invention is administered in combination with radiotherapy.

[00186] In various embodiments, the compound is administered in combination with an anti-cancer agent by administering the compounds as herein described, alone or in combination with other agents.

[00187] In various embodiments, the composition for cancer treatment of the present invention can be used together with existing chemotherapy drugs or be made as a mixture with them. Such a chemotherapy drug includes, for example, alkylating agents, nitrosourea agents, antimetabolites, antitumor antibiotics, alkaloids derived from plant, topoisomerase inhibitors, hormone therapy medicines, hormone antagonists, aromatase inhibitors, P-glycoprotein inhibitors, platinum complex derivatives, other immunotherapeutic drugs, and other anticancer agents. Further, they can be used together with hypoleukocytosis (neutrophil) medicines that are cancer treatment adjuvant, thrombopenia medicines, antiemetic drugs, and cancer pain medicines for patient's QOL recovery or be made as a mixture with them.

[00188] In various embodiments, this invention is directed to a method of destroying a cancerous cell comprising: providing a compound of this invention and contacting the cancerous cell with the compound

under conditions effective to destroy the contacted cancerous cell. According to various embodiments of destroying the cancerous cells, the cells to be destroyed can be located either *in vivo* or *ex vivo* (i.e., in culture).

[00189] In some embodiments, the cancer is selected from the group consisting of melanoma, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, Hodgkin lymphoma, glioblastoma, renal cell carcinoma, Merkel cell skin cancer (Merkel cell carcinoma), and combinations thereof. In some embodiments, the cancer is selected from the group consisting of: melanoma, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, Hodgkin lymphoma, glioblastoma, Merkel cell skin cancer (Merkel cell carcinoma), esophagus cancer; gastroesophageal junction cancer; liver cancer, (hepatocellular carcinoma); lung cancer, (small cell) (SCLC); stomach cancer; upper urinary tract cancer, (urothelial carcinoma); multiforme Glioblastoma; Multiple myeloma; anus cancer, (squamous cell); cervix cancer; endometrium cancer; nasopharynx cancer; ovary cancer; metastatic pancreas cancer; solid tumor cancer; adrenocortical Carcinoma; HTLV-1-associated adult T-cell leukemia-lymphoma; uterine Leiomyosarcoma; acute myeloid Leukemia; chronic lymphocytic Leukemia; diffuse large B-cell Lymphoma; follicular Lymphoma; uveal Melanoma; Meningioma; pleural Mesothelioma; Myelodysplasia; Soft tissue sarcoma; breast cancer; colon cancer; pancreatic cancer, Cutaneous T-cell lymphoma; peripheral T-cell lymphoma or any combination thereof.

[00190] A still further aspect of the present invention relates to a method of treating or preventing a cancerous condition that includes: providing a compound of the present invention and then administering an effective amount of the compound to a patient in a manner effective to treat or prevent a cancerous condition.

[00191] According to one embodiment, the patient to be treated is characterized by the presence of a precancerous condition, and the administering of the compound is effective to prevent development of the precancerous condition into the cancerous condition. This can occur by destroying the precancerous cell prior to or concurrent with its further development into a cancerous state.

[00192] According to other embodiments, the patient to be treated is characterized by the presence of a cancerous condition, and the administering of the compound is effective either to cause regression of the cancerous condition or to inhibit growth of the cancerous condition, i.e., stopping its growth altogether or reducing its rate of growth. This preferably occurs by destroying cancer cells, regardless of their location in the patient body. That is, whether the cancer cells are located at a primary tumor site or whether the cancer cells have metastasized and created secondary tumors within the patient body.

[00193] ACSS2 gene has recently been suggested to be associated with human alcoholism and ethanol intake. Accordingly, 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 an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective

to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

5 [00194] 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 $\leq$ 10 20-30 g/day. On the contrary, AFLD is defined as the presence of steatosis and alcohol consumption $>20-30$ g/day.

[00195] It has been shown that synthesis of metabolically available acetyl-coA from acetate is critical to the increased acetylation of proinflammatory gene histones and consequent enhancement of the inflammatory response in ethanol-exposed macrophages. This mechanism is a potential therapeutic target in acute alcoholic hepatitis.

15 [00196] Accordingly, 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 an ACSS2 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.

[00197] Accordingly, 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 an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some 25 30 35 embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[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 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 an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00199] ACSS2-mediated acetyl-CoA synthesis from acetate has also been shown to be necessary for human cytomegalovirus infection. It has been shown that glucose carbon can be converted to acetate and used to make cytosolic acetyl-CoA by acetyl-CoA synthetase short-chain family member 2 (ACSS2) for lipid synthesis, which is important for HCMV-induced lipogenesis and the viral growth. Accordingly, ACSS2 inhibitors are expected to be useful as an antiviral therapy, and in the treatment of HCMV infection.

[00200] Therefore, in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a viral infection in a subject, comprising administering a compound of this invention, to a subject suffering from a viral infection under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the viral infection in said subject. In some embodiments, the viral infection is HCMV. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00201] It was found that mice lacking ACSS2 showed reduced body weight and hepatic steatosis in a diet-induced obesity model (Z. Huang et al., "ACSS2 promotes systemic fat storage and utilization through selective regulation of genes involved in lipid metabolism" *PNAS* 115, (40), E9499-E9506, 2018).

[00202] Accordingly, in various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting a metabolic disorder in a subject, comprising administering a compound of this invention, to a subject suffering from a metabolic disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the metabolic disorder in said subject. In some embodiments, the metabolic disorder is obesity. In other embodiments, the metabolic disorder is weight gain. In other embodiments, the metabolic disorder is hepatic steatosis. In other embodiments, the metabolic disorder is fatty liver disease. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACs, ACSF2 and ACSL5. 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.

[00203] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting obesity in a subject, comprising administering a compound of this invention, to a subject suffering from obesity under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the obesity in said subject. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[00204] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting weight gain in a subject, comprising administering a compound of this invention, to a subject suffering from weight gain under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the weight gain in said subject. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[00205] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting hepatic steatosis in a subject, comprising administering a compound of this invention, to a subject suffering from hepatic steatosis under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the hepatic steatosis in said subject. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[00206] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting fatty liver disease in a subject, comprising administering a compound of this invention, to a subject suffering from fatty liver disease under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the fatty liver disease in said subject. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective

to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

5 [00207] ACSS2 is also shown to enter the nucleus under certain condition (hypoxia, high fat etc.) and to affect histone acetylation and crotonylation by making available acetyl-CoA and crotonyl-CoA and thereby regulate gene expression. For example, ACSS2 decrease is shown to lower levels of nuclear acetyl-CoA and histone acetylation in neurons affecting the the expression of many neuronal genes. In the hippocampus such redIt was found that uctions in ACSS2 lead to effects on memory and neuronal
10 plasticity (Mews P, et al., Nature, Vol 546, 381, 2017). Such epigenetic modifications are implicated in neuropsychiatric diseases such as anxiety, PTSD, depression etc. (Graff, J et al. Histone acetylation: molecular mnemonics on chromatin. Nat Rev. Neurosci. 14, 97-111 (2013)). Thus, an inhibitor of ACSS2 may find useful application in these conditions.

[00208] Accordingly, in various embodiments, this invention is directed to a method of treating,
15 suppressing, reducing the severity, reducing the risk of developing or inhibiting neuropsychiatric disease or disorder in a subject, comprising administering a compound of this invention, to a subject suffering from neuropsychiatric disease or disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the neuropsychiatric disease or disorder in said subject. In some embodiments, the neuropsychiatric disease or disorder is selected from: anxiety, depression,
20 schizophrenia, autism and/or or post-traumatic stress disorder; each represents a separate embodiment according to this invention. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some
25 embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[00209] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting anxiety in a subject, comprising administering a compound of this invention, to a subject suffering from anxiety under conditions effective to treat,
30 suppress, reduce the severity, reduce the risk of developing, or inhibit the anxiety in said subject. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. In some embodiments, the compound is any one of the
35 compounds listed in Table 1; each compound represents a separate embodiment according to this invention.

[00210] In various embodiments, this invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting depression disorder in a subject, comprising

administering a compound of this invention, to a subject suffering from depression under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the depression in said subject. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the compound is selective to ACSS1. In some
5 embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[00211] In various embodiments, this invention is directed to a method of treating, suppressing, reducing
10 the severity, reducing the risk of developing or inhibiting post-traumatic stress disorder disorder in a subject, comprising administering a compound of this invention, to a subject suffering from post-traumatic stress disorder under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the post-traumatic stress disorder in said subject. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In
15 some embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[00212] In some embodiments, this invention is directed to a method of treating, suppressing, reducing
20 the severity, reducing the risk of developing or inhibiting inflammatory condition in a subject, comprising administering a compound of this invention, to a subject suffering from inflammatory condition under conditions effective to treat, suppress, reduce the severity, reduce the risk of developing, or inhibit the inflammatory condition in said subject. In some embodiments, the compound is an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some embodiments, the
25 compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[00213] In some embodiments, this invention is directed to a method of treating, suppressing, reducing
30 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 an ACSS2 inhibitor. In some embodiments, the compound is selective to ACSS2. In some
35 embodiments, the compound is selective to ACSS1. In some embodiments, the compound is selective to both ACSS2 and ACSS1. In some embodiments, the compound is selective to ACSS2, ACSS1, AACS, ACSF2 and ACSL5. 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.

[00214] 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.

5 [00215] 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 cancer cells or precancerous cells are present. Thus, administering can be accomplished in any manner effective for delivering the compounds or the pharmaceutical compositions to the cancer cells or precancerous cells. Exemplary modes of administration include, without limitation, administering the compounds or
 10 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.

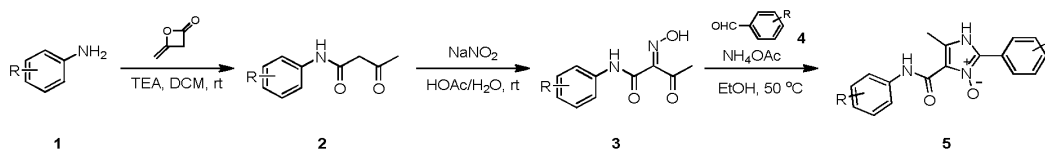
[00216] The following examples are presented in order to more fully illustrate the preferred
 15 embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention.

EXAMPLES

EXAMPLE 1

20 Synthetic Details for Compounds of the Invention

General Scheme



General procedure of 3-oxo-N-phenylbutanamide (2)

[00217] To a solution of aniline 1 (1.0 eq.) and triethyl amine (1.0 eq.) in dichloromethane was added
 25 4-methyleneoxetan-2-one (1.1 eq.). The solution was stirred at room temperature for 1 h ~ 14 h. Simple aqueous work-up afforded the product with good purity and yield. If the reaction didn't work well, purification by reversed phase chromatography was necessary.

General procedure of (E)-2-(hydroxyimino)-3-oxo-N-phenylbutanamide (3)

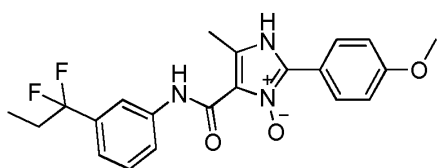
30 [00218] To a solution of 3-oxo-N-phenylbutanamide in acetic acid was added the aqueous solution of sodium nitrite (1.1 eq.) at 0 °C. The reaction was stirred at room temperature for 0.5 h and then concentrated in vacuum. This reaction usually worked well. The crude was used directly for next step without work-up and purification.

General procedure of 5-methyl-2-phenyl-4-(phenylcarbamoyl)-1H-imidazole 3-oxide (5)

[00219] A mixture of (*E*)-2-(hydroxyimino)-3-oxo-N-phenylbutanamide (1.0 eq.), aromatic aldehyde (1.0 eq.) and ammonium acetate (4 eq.) in ethanol was heated at 50 °C for 1 h. Then concentrated the solution and purified the crude by prep-HPLC to obtain the desired target.

Synthesis of 101

[00220] **Step 1: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxyphenyl)-5-methyl-1H-imidazole 3-oxide (101)**



10 [00221] **101** was obtained *via* general procedure from **103-G** and 4-methoxybenzaldehyde.

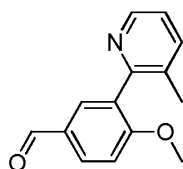
[00222] **LCMS:** (ESI) *m/z*: 402.1 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ : 13.77 (s, 1H), 13.21 (s, 1H), 8.39 (d, *J* = 8.4 Hz, 2H), 7.93 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 2.60 (s, 3H), 2.27-2.17 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H).

15 [00223] 5.95 mmol, 1.0 *eq*) in *N,N*-dimethylformamide (18 mL) was added drop wise at 25 °C. Then the reaction mixture was warmed to 100 °C and stirred for 1 h under nitrogen atmosphere. The reaction mixture was cooled to 25 °C, then the reaction mixture was poured into ice water (20 mL), basified to pH ~ 10 with saturated sodium bicarbonate, extracted with ethyl acetate (30 mL x 3). The organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtrated and the filtrate was
20 concentrated under reduced pressure. The residue was purified by silica gel (column chromatography (petroleum ether/ethyl acetate = 5/1) to give 0.35g (32 % yield) of **101-B** as a yellow solid.

[00224] **LCMS:** (ESI) *m/z*: 186.8 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃-*d*) δ : 8.52 (s, 1H), 4.02 (s, 3H), 2.86 (s, 3H).

Synthesis of 100

25 **Step 1: Synthesis of 4-methoxy-3-(3-methylpyridin-2-yl)benzaldehyde (100-A)**

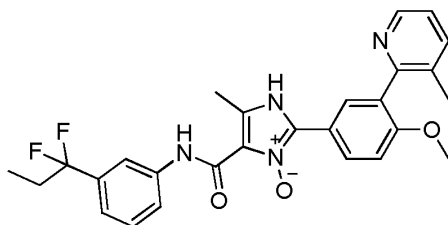


[00225] To a solution of 2-bromo-3-methyl-pyridine (500 mg, 2.91 mmol, 1.0 *eq*) and (5-formyl-2-

methoxy-phenyl)boronic acid (628 mg, 3.49 mmol, 1.2 *eq*) and potassium carbonate (803 mg, 5.81 mmol, 2.0 *eq*) in *N,N*-dimethylformamide (20 mL) was added tetrakis(triphenylphosphine)palladium (168 mg, 145 μ mol, 0.050 *eq*). The mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. Then the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/3) to give 560 mg (85% yield) of **100-A** as a colorless oil.

[00226] $^1\text{H NMR}$ (400 MHz, CDCl_3-d) δ : 9.94 (s, 1H), 8.53 (dd, $J=1.2, 4.8$ Hz, 1H), 7.97 (dd, $J=2.0, 8.4$ Hz, 1H), 7.83 (d, $J=2.4$ Hz, 1H), 7.59 (dd, $J=0.8, 8.0$ Hz, 1H), 7.24 (dd, $J=4.8, 7.6$ Hz, 1H), 7.11 (d, $J=8.4$ Hz, 1H), 3.88 (s, 3H), 2.16 (s, 3H).

10 **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-3-(3-methylpyridin-2-yl)phenyl)-5-methyl-1*H*-imidazole 3-oxide (100)**

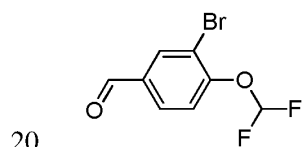


[00227] **100** was obtained via general procedure from **100-A** and **103-G**

[00228] **LCMS**: (ESI) m/z : 493.2 $[\text{M}+\text{H}]^+$. $^1\text{H NMR}$ (400 MHz, $\text{MeOD}-d_4$) δ : 8.47 (dd, $J=2.4, 8.8$ Hz, 1H), 8.42 (d, $J=4.0$ Hz, 1H), 8.12 (d, $J=2.4$ Hz, 1H), 7.92 (s, 1H), 7.82-7.75 (m, 1H), 7.70 (d, $J=8.0$ Hz, 1H), 7.45 (t, $J=8.0$ Hz, 1H), 7.38 (dd, $J=5.2, 7.6$ Hz, 1H), 7.35 (d, $J=9.2$ Hz, 1H), 7.25 (d, $J=7.6$ Hz, 1H), 3.89 (s, 3H), 2.67 (s, 3H), 2.24-2.16 (m, 5H), 0.99 (t, $J=7.6$ Hz, 3H).

Synthesis of 103

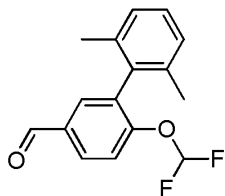
Step 1: Synthesis of 3-bromo-4-(difluoromethoxy)benzaldehyde (103-A)



[00229] To a solution of 3-bromo-4-hydroxy-benzaldehyde (500 mg, 2.49 mmol, 1.0 *eq*) in *N,N*-dimethylformamide (5 mL) were added sodium carbonate (527 mg, 4.97 mmol, 2.0 *eq*) and sodium;2-chloro-2,2-difluoro-acetate (758 mg, 4.97 mmol, 2.0 *eq*). The reaction was stirred at 100 °C for 2 h. Then the mixture was diluted with water (30 mL) and the pH was adjusted to 7 with hydrochloric acid (1 M). Then it was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 450 mg (crude) of **103-A** as a colorless oil.

[00230] $^1\text{H NMR}$ (400Hz, $\text{DMSO-}d_6$): 9.52 (s, 1H), 8.25 (s, 1H), 7.98 (t, $J = 1.6$ Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.52 (t, $J = 32.4$ Hz, 1H).

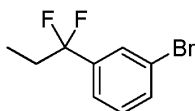
Step 2: Synthesis of 6-(difluoromethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (103-B)



- 5 [00231] A mixture of **103-A** (110 mg, 438 μmol 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (98.6 mg, 657 μmol , 1.5 *eq*), tetrakis(triphenylphosphine)palladium (50.6 mg, 43.8 μmol , 0.10 *eq*) and potassium phosphate (279 mg, 1.31 mmol, 3.0 *eq*) in 1,2-dimethoxyethane (2.5 mL) and water (0.5 mL) was degassed and purged with nitrogen for 3 times. The mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL).
- 10 The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 90.0 mg (74% yield) of **103-B** as a light yellow oil.

- [00232] $^1\text{H NMR}$ (400 MHz, CDCl_3 -*d*) δ : 10.02 (s, 1H), 7.94 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.72 (d, $J = 2.0$ Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.21-7.25 (m, 1H), 7.14 (d, $J = 8.0$ Hz, 2H), 6.44 (t, $J = 72.8$ Hz, 1H), 2.02 (s, 6H).
- 15

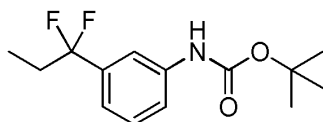
Step 3: Synthesis of 1-bromo-3-(1,1-difluoropropyl)benzene (103-C)



- [00233] A solution of 1-(3-bromophenyl)propan-1-one (25.0 g, 117 mmol, 1.0 *eq*) and diethylaminosulfur trifluoride (94.6 g, 587 mmol, 78 mL, 5.0 *eq*) in chloroform (400 mL) was stirred under nitrogen atmosphere at 70 °C for 12 h. The reaction mixture was quenched with ice water (1 L), and the aqueous layer was extracted with dichloromethane (300 mL x 3). The combined organic layer was washed with brine (1.0 L), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 8/1) to give 21.0 g (76% yield) of **103-C** as a light yellow oil.
- 20
- 25

[00234] $^1\text{H NMR}$ (400 MHz, CDCl_3 -*d*) δ : 7.63 (s, 1H), 7.57 (dd, $J = 8.0, 0.4$ Hz, 1H), 7.41 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.31 (t, $J = 7.6$ Hz, 1H), 2.19-2.09 (m, 2H), 1.00 (t, $J = 7.6$ Hz, 3H).

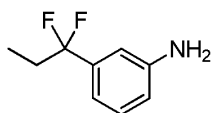
Step 4: Synthesis of *tert*-butyl (3-(1,1-difluoropropyl)phenyl)carbamate (103-D)



- [00235] A suspension of **103-C** (21.0 g, 89.3 mmol, 1.0 *eq*), *tert*-butyl carbamate (15.7 g, 134 mmol, 1.5 *eq*), palladium acetate (1.00 g, 4.47 mmol, 0.050 *eq*), dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphane (8.52 g, 17.9 mmol, 0.20 *eq*), cesium carbonate (58.2 g, 179 mmol, 2.0 *eq*) in dioxane (400 mL) was degassed and purged with nitrogen several times, then the reaction mixture was stirred under nitrogen atmosphere at 90 °C for 12 h. The reaction was filtered, and the filtrate was diluted with water (300 mL). The aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 24.0 g (75% yield) of **103-D** as a yellow oil.

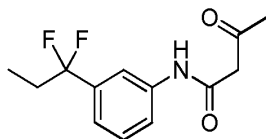
[00236] **LCMS:** (ESI) *m/z*: 172.1 [M-Boc+H]⁺.

Step 5: Synthesis of 3-(1,1-difluoropropyl)aniline (103-E)



- [00237] A solution of **103-D** (24.0 g, 75.2 mmol, 1.0 *eq*) in hydrogen chloride in ethyl acetate (4 M, 200 mL) was stirred at 25 °C for 30 min. The pH of the mixture was adjusted to 8-9 by saturated aqueous sodium hydroxide (2.0 M). The resulting mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 14.0 g (crude) of **103-E** as a yellow oil.
- [00238] **¹H NMR** (400 MHz, CDCl₃-*d*) δ: 7.20 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.80 (s, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 3.49 (s, 2H), 2.17-2.07 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H). **¹⁹F NMR** (376 MHz, CDCl₃-*d*) δ: -97.66.

Step 6: Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-3-oxobutanamide (103-F)

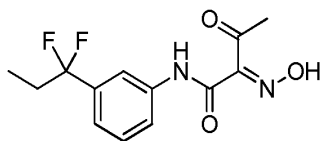


- [00239] **103-F** was obtained via general procedure from **103-E**.

[00240] **LCMS:** (ESI) *m/z*: 256.4 [M+H]⁺.

Step 7: Synthesis of (*E*)-*N*-(3-(1,1-difluoropropyl)phenyl)-2-(hydroxyimino)-3-oxobutanamide

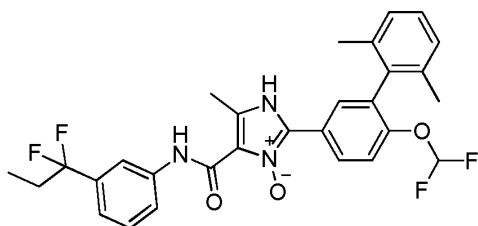
(103-G)



[00241] **103-G** was obtained via general procedure from **103-F**.

[00242] **LCMS**: (ESI) m/z : 285.2 $[M+H]^+$.

5 **Step 8: Synthesis of 2-(6-(difluoromethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (103)**

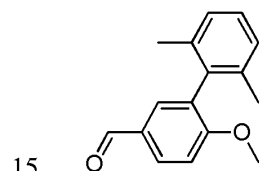


[00243] **103** was obtained via general procedure from **103-G** and **103-B**.

10 [00244] **LCMS**: (ESI) m/z : 542.2 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 8.40 (dd, J = 8.8, 2.0 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.92 (s, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.19-7.22 (m, 1H), 7.13-7.14 (m, 2H), 6.83 (t, J = 73.2 Hz, 1H), 2.67 (s, 3H), 2.12-2.25 (m, 2H), 2.05 (s, 6H), 0.98 (t, J = 7.2 Hz, 3H).

Synthesis of 102

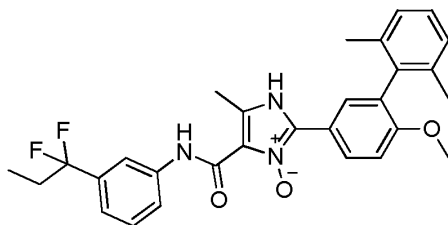
Step 1: Synthesis of 6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (102-A)



20 [00245] A mixture of 3-bromo-4-methoxy-benzaldehyde (500 mg, 2.33 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (523 mg, 3.49 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (672 mg, 581 μ mol, 0.25 *eq*), potassium phosphate (987 mg, 4.65 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (10 mL) and water (2 mL) was degassed and purged with nitrogen for 3 times. The mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 30/1) to give 160 mg (29% yield) of **102-A** as colourless oil.

[00246] ¹H NMR (400 MHz, CDCl₃-d) δ: 9.93 (s, 1H), 7.92 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.15-7.10 (m, 3H), 3.85 (s, 3H), 2.00 (s, 6H).

Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (102)

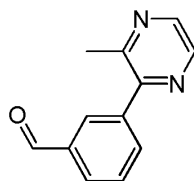


[00247] **102** was obtained via general procedure from **103-G** and **102-A**.

[00248] **LCMS:** (ESI) *m/z*: 506.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ: 8.38 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.94-7.89 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.17-7.12 (m, 1H), 7.12-7.08 (m, 2H), 3.84 (s, 3H), 2.66 (s, 3H), 2.24-2.14 (m, 2H), 2.02 (s, 6H), 0.98 (t, *J* = 7.6 Hz, 3H).

Synthesis of 110

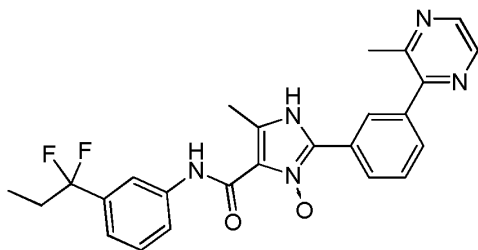
Step 1: Synthesis of 3-(3-methylpyrazin-2-yl)benzaldehyde (110-A)



[00249] A mixture of 2-chloro-3-methyl-pyrazine (200 mg, 1.56 mmol, 1.0 *eq*), (3-formylphenyl)boronic acid (233 mg, 1.56 mmol, 1.0 *eq*), tetrakis(triphenylphosphine)palladium (179 mg, 155 μmol, 0.10 *eq*), potassium phosphate (660 mg, 3.02 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (10 mL) and water (2 mL) was degassed and purged with nitrogen for 3 times. The mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 230 mg (72% yield) of **110-A** as a colorless oil.

[00250] **LCMS:** (ESI) *m/z*: 199.1 [M+H]⁺.

Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-2-(3-(3-methylpyrazin-2-yl)phenyl)-1*H*-imidazole 3-oxide (110)

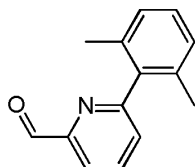


[00251] **110** was obtained *via* general procedure from **103-G** and **110-A**

[00252] **LCMS:** (ESI) m/z : 464.2 $[M+H]^+$. **¹H NMR** (400Hz, MeOD- d_4) δ : 8.60-8.53 (m, 3H), 8.35-8.33 (m, 1H), 7.92 (s, 1H), 7.80-7.70 (m, 3H), 7.47-7.43 (m, 1H), 7.24 (d, J = 7.6 Hz, 1H), 2.68 (s, 6H),
5 2.24-2.14 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H).

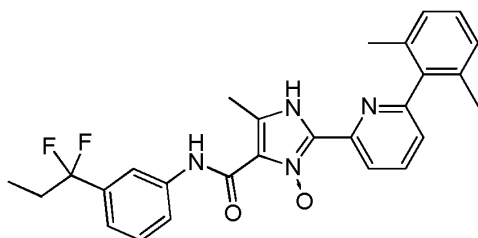
Synthesis of 111

Step 1: Synthesis of 3-bromo-4-(difluoromethoxy)benzaldehyde (111-A)



[00253] **111-A** was obtained *via* similar procedure of **102-A** from 6-bromopicolinaldehyde and (2,6-dimethylphenyl)boronic acid.
10

Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-(2,6-dimethylphenyl)pyridin-2-yl)-5-methyl-1H-imidazole 3-oxide (111)

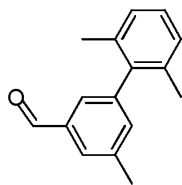


[00254] **111** was obtained *via* general procedure from **111-A** and **103-G**.

15 [00255] **LCMS:** (ESI) m/z : 477.2 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 9.01 (d, J = 8.0 Hz, 1H), 8.10 (t, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.41 (dd, J = 7.6, 0.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.20-7.23 (m, 1H), 7.13 (d, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.16-2.25 (m, 2H), 2.06 (s, 6H), 1.00 (t, J = 7.2 Hz, 3H).

Synthesis of 106

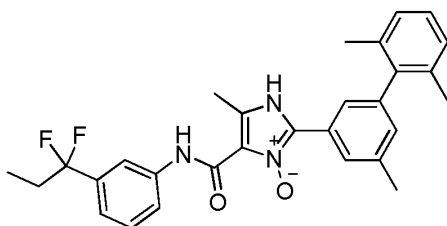
20 Step 1: Synthesis of 3-(2,6-dimethylphenyl)-5-methyl-benzaldehyde (106-A)



[00256] A mixture of 3-bromo-5-methyl-benzaldehyde (200 mg, 1.00 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (227 mg, 1.51 mmol, 1.5 *eq*), tetrakis[triphenylphosphine]palladium (581 mg, 503 μ mol, 0.5 *eq*), potassium phosphate (640 mg, 3.02 mmol, 3.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was degassed and purged with nitrogen for 3 times. The mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. Then the reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 190 mg (crude) of **106-A** as a yellow oil.

[00257] **LCMS:** (ESI) m/z : 225.2 [M+H]⁺.

Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-2-(2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-1H-imidazole 3-oxide (106)

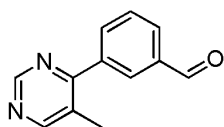


[00258] **106** was obtained via general procedure from **103-G** and **106-A**.

[00259] **LCMS:** (ESI) m/z : 490.4 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.13 (s, 1H), 7.92 (s, 1H), 7.83 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.17-7.10 (m, 4H), 2.67 (s, 3H), 2.51 (s, 3H), 2.23-2.16 (m, 2H), 2.05 (s, 6H), 0.98 (t, J = 7.6 Hz, 3H).

20 **Synthesis of 109**

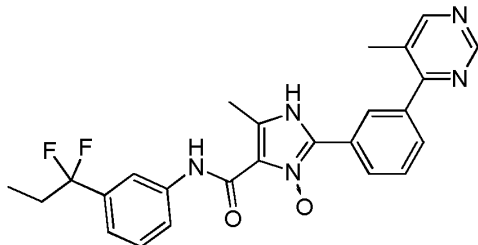
[00260] **Step 1: Synthesis of 3-(5-methylpyrimidin-4-yl)benzaldehyde (109-A)**



[00261] **109-A** was obtained *via* similar procedure of **106-A** from 4-chloro-5-methyl-pyrimidine and (3-formylphenyl)boronic acid.

[00262] **LCMS:** (ESI) m/z : 199.2 $[M+H]^+$.

[00263] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-2-(3-(5-methylpyrimidin-4-yl)phenyl)-1H-imidazole 3-oxide (109)**

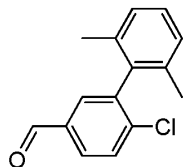


5 [00264] **109** was obtained *via* general procedure from **103-G** and **109-A**.

[00265] **LCMS:** (ESI) m/z : 464.2 $[M+H]^+$. **¹H NMR** (400Hz, DMSO- d_6): δ : 1.58 (s, 2H), 9.14 (s, 1H), 8.80 (s, 1H), 8.76 (s, 1H), 8.54 (d, $J = 7.6$ Hz, 1H), 7.94 (s, 1H), 7.78 (s, 1H), 7.72 (t, $J = 8.0$ Hz, 2H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 2.62 (s, 3H), 2.41 (s, 3H), 2.15-2.07 (m, 2H), 0.93 (t, $J = 7.6$ Hz, 3H).

10 **Synthesis of 108**

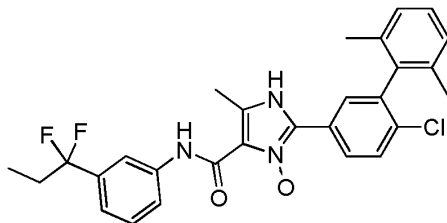
[00266] **Step 1: Synthesis of 6-chloro-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (108-A)**



[00267] **108-A** was obtained *via* similar procedure of **102-A** from 3-bromo-4-chlorobenzaldehyde and (2,6-dimethylphenyl)boronic acid.

15 [00268] **LCMS:** (ESI) m/z : 245.0 $[M+H]^+$.

[00269] **Step 2: Synthesis of 2-(6-chloro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (108)**



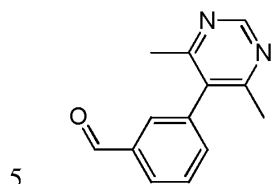
[00270] **108** was obtained *via* general procedure from **103-G** and **108-A**.

20 [00271] **LCMS:** (ESI) m/z : 510.2 $[M+H]^+$. **¹H NMR** (400Hz, DMSO- d_6): δ : 13.49 (brs, 1H), 13.39 (brs, 1H), 8.53 (d, $J = 8.8$ Hz, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz,

1H), 7.47-7.43 (m, 1H), 7.28-7.18 (m, 4H), 2.59 (s, 3H), 2.28-2.13 (m, 2H), 1.98 (s, 6H), 0.92 (t, $J = 7.6$ Hz, 3H).

Synthesis of 112

[00272] **Step 1: Synthesis of 3-(4,6-dimethylpyrimidin-5-yl)benzaldehyde (112-A)**

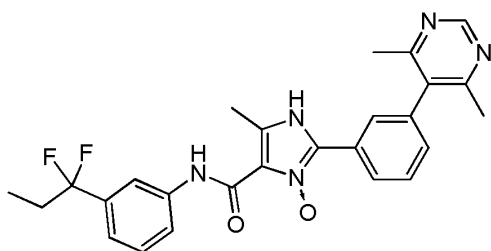


[00273] **112-A** was obtained *via* similar procedure of **102-A** from 5-bromo-4,6-dimethylpyrimidine and (3-formylphenyl)boronic acid.

[00274] **LCMS:** (ESI) m/z : 213.0 $[M+H]^+$.

[00275] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(3-(4,6-dimethylpyrimidin-5-yl)phenyl)-5-methyl-1H-imidazole 3-oxide (112)**

10



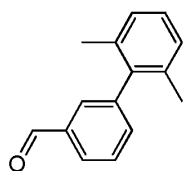
[00276] **112** was obtained *via* general procedure from **103-G** and **112-A**.

[00277] **LCMS:** (ESI) m/z : 478.2 $[M+H]^+$. **¹H NMR** (400Hz, MeOD- d_4) δ : 8.90 (s, 1H), 8.32 (s, $J = 8.0$ Hz, 1H), 8.26 (d, $J = 1.2$ Hz, 1H), 7.91 (s, 1H), 7.78-7.69 (m, 2H), 7.48-7.43 (m, 2H), 7.25 (d, $J = 8.0$ Hz, 1H), 2.70 (s, 3H), 2.34 (s, 6H), 2.24-2.14 (m, 2H), 0.98 (t, $J = 7.2$ Hz, 3H).

15

Synthesis of 107

[00278] **Step 1: Synthesis of 2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (107-A)**

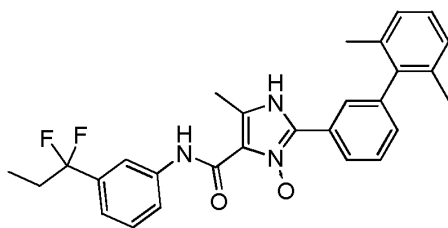


[00279] **107-A** was obtained *via* similar procedure of **102-A** from 3-bromobenzaldehyde and (2,6-dimethylphenyl)boronic acid.

20

[00280] **LCMS:** (ESI) m/z : 211.0 $[M+H]^+$.

[00281] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (107)**

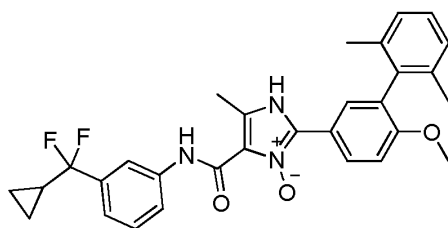


[00282] **107** was obtained *via* general procedure from **103-G** and **107-A**.

- 5 [00283] **LCMS:** (ESI) m/z : 510.2 $[M+H]^+$. **1H NMR** (400Hz, DMSO- d_6) δ : 13.63 (brs, 1H), 13.31 (brs, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.26 (s, 1H), 7.95 (s, 1H), 7.72-7.65 (m, 2H), 7.46-7.44 (m, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.24-7.16 (m, 4H), 2.61 (s, 3H), 2.29-2.15 (m, 2H), 2.02 (s, 6H), 0.93 (t, J = 7.6 Hz, 3H).

Synthesis of 104

- 10 [00284] **Step 1: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (104)**

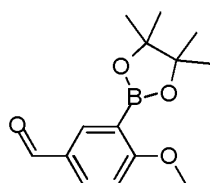


[00285] **107** was obtained *via* general procedure from **161-E** and **102-A**.

- 15 [00286] **LCMS:** (ESI) m/z : 518.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.38 (dd, J = 2.4, 8.8 Hz, 1H), 7.98 (s, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.33-7.29 (m, 2H), 7.17-7.13 (m, 1H), 7.11-7.07 (m, 2H), 3.84 (s, 3H), 2.66 (s, 3H), 2.02 (s, 6H), 1.66-1.55 (m, 1H), 0.74-0.68 (m, 4H).

Synthesis of 105

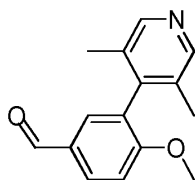
- 20 [00287] **Step 1: Synthesis of 4-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (105-A)**



[00288] To a solution of 3-bromo-4-methoxy-benzaldehyde (200 mg, 930 μmol , 1.0 *eq*) in dioxane (5 mL) were added potassium acetate (274 mg, 2.79 mmol, 3.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (69.0 mg, 94.3 μmol , 0.1 *eq*) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (354 mg, 1.40 mmol, 1.5 *eq*). The reaction mixture was stirred at 90 °C for 6 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. Then it was diluted with water 10 mL, extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 250 mg (crude) of **105-A** as a brown oil.

[00289] **LCMS:** (ESI) m/z : 263.1 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, CDCl_3 -*d*) δ : 9.91 (s, 1H), 8.21 (d, J = 2.4 Hz, 1H), 7.97 (dd, J = 2.0, 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 1.38 (s, 12H).

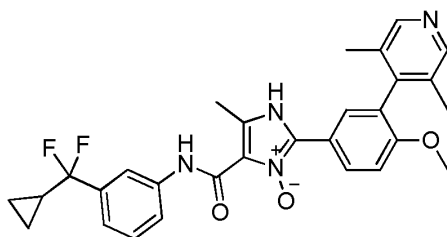
[00290] **Step 2: Synthesis of 3-(3,5-dimethyl-4-pyridyl)-4-methoxy-benzaldehyde (105-B)**



[00291] To a solution of **105-A** (100 mg, 381 μmol , 1.0 *eq*) and 4-bromo-3,5-dimethyl-pyridine (71.0 mg, 381 μmol , 1.0 *eq*) in dioxane (5 mL) and water (1 mL) were added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (28.0 mg, 38.3 μmol , 0.10 *eq*) and sodium carbonate (81.0 mg, 764 μmol , 2.0 *eq*). The reaction mixture was stirred at 90 °C for 4 h. Then the reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give 40.0 mg (43% yield) of **105-B** as a yellow solid.

[00292] **LCMS:** (ESI) m/z : 242.2 $[\text{M}+\text{H}]^+$.

[00293] **Step 3: Synthesis of 4-((3-(cyclopropyl)difluoromethyl)phenyl)carbamoyl)-2-(3-(3,5-dimethylpyridin-4-yl)-4-methoxyphenyl)-5-methyl-1H-imidazole 3-oxide (106)**

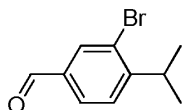


[00294] **105** was obtained *via* general procedure from **161-E** and **105-B**.

[00295] **LCMS**: (ESI) m/z : 519.4 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.39 (dd, $J = 2.4, 8.8$ Hz, 1H), 8.29 (s, 2H), 8.02 (d, $J = 2.0$ Hz, 1H), 7.97 (s, 1H), 7.69 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 1H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.29 (d, $J = 7.6$ Hz, 1H), 3.86 (s, 3H), 2.64 (s, 3H), 2.08 (s, 6H), 1.69-1.53 (m, 1H), 0.73-0.68 (m, 4H).

Synthesis of 117

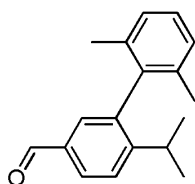
[00296] Step 1: Synthesis of 3-bromo-4-isopropylbenzaldehyde (117-A)



[00297] To a solution of 4-isopropylbenzaldehyde (5.00 g, 33.7 mmol, 1.0 *eq*) in sulfuric acid (50 mL) was added 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione (7.72 g, 27.0 mmol, 0.80 *eq*) in 6 portions at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Then the mixture was quenched by slow addition to ice water (100 mL). The mixture was basified to pH>7 by aqueous sodium hydroxide (2 M). The resulting mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 1.30 g (17% yield) of **117-A** as a yellow oil.

[00298] **1H NMR** (400 MHz, $CDCl_3$ - d) δ : 9.92 (s, 1H), 8.04 (d, $J=1.6$ Hz, 1H), 7.79 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 1H), 3.47-3.40 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H).

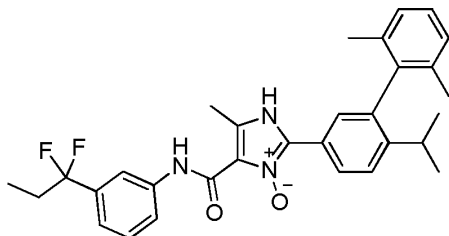
[00299] Step 2: Synthesis of 6-isopropyl-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (117-B)



[00300] To a solution of **117-A** (200 mg, 881 μ mol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (198 mg, 1.32 mmol, 1.5 *eq*), potassium phosphate (374 mg, 1.76 mmol, 2.0 *eq*) and dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (72.3 mg, 176 μ mol, 0.20 *eq*) in toluene (5 mL) was added tri(dibenzylideneacetone)dipalladium(0) (80.7 mg, 88.1 μ mol, 0.10 *eq*). The mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. Then the mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10/1) to give 180 mg (72% yield) of **117-B** as a yellow oil.

[00301] LCMS: (ESI) m/z : 253.4 [M+H]⁺.

[00302] **Step 3: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-isopropyl-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (117)**

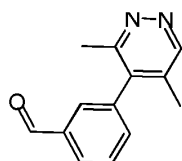


5 [00303] **117** was obtained *via* general procedure from **117-B** and **103-G**.

[00304] LCMS: (ESI) m/z : 518.3 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 8.30 (dd, J = 2.0, 8.4 Hz, 1H), 7.94-7.86 (m, 2H), 7.72-7.66 (m, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.27-7.13 (m, 4H), 2.66 (s, 3H), 2.65-2.61 (m, 1H), 2.25-2.11 (m, 2H), 2.01 (s, 6H), 1.17 (d, J = 6.8 Hz, 6H), 0.98 (t, J = 7.2 Hz, 3H).

Synthesis of 116

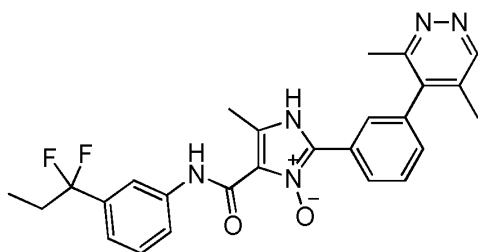
10 [00305] **Step 1: Synthesis of 3-(3,5-dimethylpyridazin-4-yl)benzaldehyde (116-A)**



[00306] **116-A** was obtained *via* similar procedure of **102-A** from 4-chloro-3,5-dimethylpyridazine and (3-formylphenyl)boronic acid.

[00307] LCMS: (ESI) m/z : 213.1 [M+H]⁺.

15 [00308] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(3-(3,5-dimethylpyridazin-4-yl)phenyl)-5-methyl-1H-imidazole 3-oxide (116)**



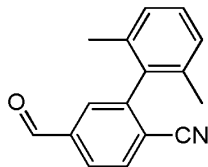
[00309] **116** was obtained *via* general procedure from **103-G** and **116-A**.

[00310] LCMS: (ESI) m/z : 478.2 [M+H]⁺. ¹H NMR (400Hz, DMSO-*d*₆) δ : 13.43 (s, 1H), 9.22 (s, 1H), 8.48 (d, J = 12.8 Hz, 1H), 8.42 (s, 1H), 7.91 (s, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.48-7.46 (m, 2H), 7.22 (d, J = 7.6 Hz, 1H), 2.62 (s, 3H), 2.43 (s, 3H), 2.26-2.17 (m, 2H), 2.16 (s, 3H),

0.92 (t, $J = 7.2$ Hz, 3H).

Synthesis of 114

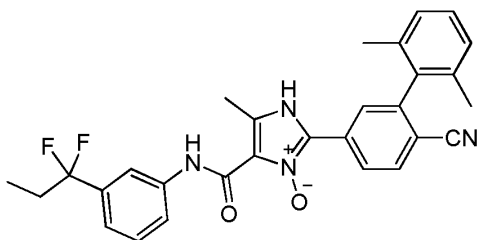
[00311] **Step 1: Synthesis of 5-formyl-2',6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (114-A)**



5 [00312] **114-A** was obtained *via* similar procedure of **102-A** from 2-bromo-4-formylbenzonitrile and (2,6-dimethylphenyl)boronic acid.

[00313] ^1H NMR (400Hz, CDCl_3-d) δ : 10.13 (s, 1H), 8.01-7.95 (m, 2H), 7.82 (s, 1H), 7.30-7.27 (m, 1H), 7.18 (d, $J = 7.6$ Hz, 2H), 2.03 (s, 6H).

[00314] **Step 2: Synthesis of 2-(6-cyano-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (114)**

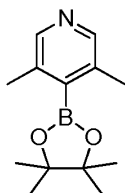


[00315] **114** was obtained *via* general procedure from **103-G** and **114-A**.

[00316] **LCMS**: (ESI) m/z : 501.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400Hz, $\text{DMSO}-d_6$) δ : 13.57 (s, 1H), 13.30 (s, 1H), 8.69 (d, $J = 7.6$ Hz, 1H), 8.45 (s, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 7.95 (s, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.46 (t, $J = 8.0$ Hz, 1H), 7.29-7.25 (m, 1H), 7.23 (s, 3H), 2.62 (s, 3H), 2.28-2.20 (m, 2H), 2.01 (s, 6H), 0.92 (t, $J = 7.6$ Hz, 3H).

Synthesis of 115

[00317] **Step 1: 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (115-A)**

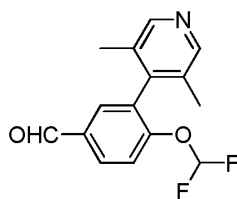


20 [00318] To a solution of 4-bromo-3,5-dimethyl-pyridine (200 mg, 1.07 mmol, 1.0 *eq*) in dioxane (5 mL) were added potassium acetate (211 mg, 2.15 mmol, 2.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (409 mg, 1.61 mmol, 1.5 *eq*) and 4,4,5,5-

tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (354 mg, 1.40 mmol, 1.5 eq). The reaction mixture was stirred at 90 °C for 6 h under nitrogen atmosphere. Then the reaction mixture was concentrated under reduced pressure to give a residue. It was diluted with water 10 mL, extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine 30 mL, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 200 mg (79%) of **115-A** as a brown oil.

[00319] **LCMS:** (ESI) m/z : 234.2 [M+H]⁺

[00320] **Step 2: Synthesis of 4-(difluoromethoxy)-3-(3,5-dimethyl-4-pyridyl)benzaldehyde (115-B)**

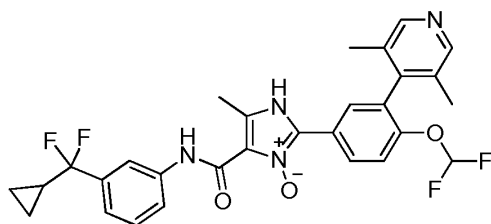


10

[00321] To a solution of **115-A** (100 mg, 381 umol, 1.0 eq) and **103-A** (80.0 mg, 381 umol, 1.0 eq) in dioxane (5 mL) and water (1 mL) were added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (28.0 mg, 38.3 umol, 0.10 eq) and sodium carbonate (81.0 mg, 764 umol, 2.0 eq). The reaction mixture was stirred at 90 °C for 4 h. The reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give 40.0 mg (43% yield) of **115-B** as a yellow solid.

20 [00322] **LCMS:** (ESI) m/z : 278.9 [M+H]⁺.

[00323] **Step 3: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(4-(difluoromethoxy)-3-(3,5-dimethylpyridin-4-yl)phenyl)-5-methyl-1H-imidazole 3-oxide (115)**



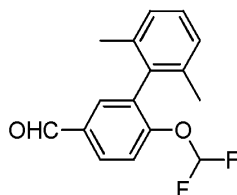
[00324] **115** was obtained *via* general procedure from **161-E** and **115-B**.

25 [00325] **LCMS:** (ESI) m/z : 555.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 8.70 (s, 2H), 8.43 (d, J = 2.0 Hz, 1H), 8.37 (dd, J = 2.0, 8.8 Hz, 1H), 7.92 (s, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz,

1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.06 (t, $J = 73.2$ Hz, 1H), 2.71 (s, 3H), 2.29 (s, 6H), 1.66-1.53 (m, 1H), 0.73-0.68 (m, 4H).

Synthesis of 113

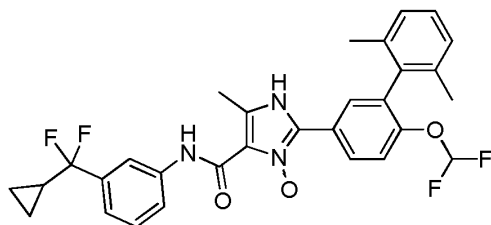
[00326] **Step 1: Synthesis of 4-(difluoromethoxy)-3-(2,6-dimethylphenyl)benzaldehyde (113-A)**



[00327] A mixture of **103-A** (200 mg, 796 μ mol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (179 mg, 1.20 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (92.0 mg, 79.6 μ mol, 0.10 *eq*), potassium phosphate (338 mg, 1.59 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. Then the reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 150 mg (68% yield) of **113-A** as colorless oil.

[00328] **LCMS:** (ESI) m/z : 277.1 $[M+H]^+$.

[00329] **Step 2: Synthesis of N-[3-[cyclopropyl(difluoro)methyl]phenyl]-2-[4-(difluoromethoxy)-3-(2,6-dimethylphenyl)phenyl]-5-methyl-3-oxido-1H-imidazol-3-ium-4-carboxamide (113)**

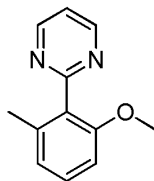


[00330] **113** was obtained *via* general procedure from **161-E** and **113-A**.

[00331] **LCMS:** (ESI) m/z : 554.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.41 (dd, $J = 2.4, 8.8$ Hz, 1H), 8.10 (d, $J = 2.4$ Hz, 1H), 7.98 (s, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 7.6$ Hz, 1H), 7.23-7.19 (m, 1H), 7.16-7.11 (m, 2H), 6.84 (t, $J = 73.2$ Hz, 1H), 2.68 (s, 3H), 2.05 (s, 6H), 1.65-1.55 (m, 1H), 0.74-0.67 (m, 4H).

Synthesis of 118

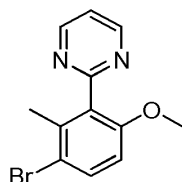
[00332] **Step 1: Synthesis of 2-(2-methoxy-6-methyl-phenyl)pyrimidine (118-A)**



[00333] A mixture of **144-A** (200 mg, 1.20 mmol, 1.1 *eq*), 2-bromopyrimidine (165 mg, 1.10 mmol, 1.0 *eq*), tetrakis[triphenylphosphine]palladium (127 mg, 110 μ mol, 0.10 *eq*), sodium carbonate (232 mg, 2.19 mmol, 2.0 *eq*) and water (0.5 mL) in 1,2-dimethoxyethane (2.5 mL) was stirred at 100 °C for 12 hr under nitrogen atmosphere. Then the mixture was concentrated in vacuum to give the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 140 mg (59% yield) of **118-A** as a yellow solid.

[00334] **LCMS:** (ESI) m/z : 201.2 $[M+H]^+$. **1H NMR** (400 MHz, $CDCl_3-d$) δ : 8.89 (d, J = 5.0 Hz, 2 H,), 7.25-7.32 (m, 2 H), 6.87 (dd, J = 20.0, 8.0 Hz, 2 H), 2.09 (s, 3 H), 3.74 (s, 3 H).

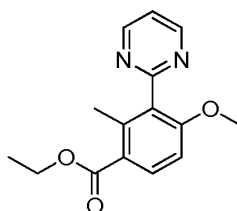
10 [00335] **Step 2: Synthesis of 2-(3-bromo-6-methoxy-2-methyl-phenyl)pyrimidine (118-B)**



[00336] To a solution of **118-A** (140 mg, 650 μ mol, 1.0 *eq*) in acetonitrile (2 mL) was added 1-bromopyrrolidine-2,5-dione (127 mg, 715 μ mol, 1.1 *eq*). The mixture was stirred at 25 °C for 2 h. The mixture was poured into saturated sodium sulfite (20 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layer was washed brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give 180 mg (94% yield) of **118-B** as a yellow solid

[00337] **LCMS:** (ESI) m/z : 280.2 $[M+H]^+$.

[00338] **Step 3: Synthesis of ethyl 4-methoxy-2-methyl-3-pyrimidin-2-yl-benzoate (118-C)**

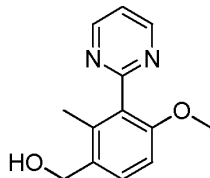


20 [00339] A mixture of **118-B** (180 mg, 613 μ mol, 1.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (672 mg, 918 μ mol, 1.5 *eq*) and triethylamine (186 mg, 1.84 mmol, 3.0 *eq*) in ethanol (5 mL) was stirred at 70 °C for 36 h under carbonic oxide atmosphere (50 Psi). The mixture was concentrated in vacuum to give the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 90 mg (54%

yield) of **118-C** as a yellow liquid.

[00340] **LCMS:** (ESI) m/z : 273.1 [M+H]⁺.

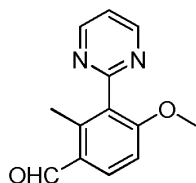
[00341] **Step 4: Synthesis of (4-methoxy-2-methyl-3-pyrimidin-2-yl-phenyl)methanol (118-D)**



- 5 [00342] To a solution of **118-C** (90.0 mg, 310 μ mol, 1.0 *eq*) in tetrahydrofuran (2 mL) was added diisobutyl aluminum hydride (1 M, 1.2 mL, 4.0 *eq*) at 0°C. The reaction was stirred at 25 °C for 12 h. Then the reaction was quenched by adding saturated ammonium chloride (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL x 2). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 70.0
- 10 mg (91% yield) of **118-D** as a yellow solid.

[00343] **LCMS:** (ESI) m/z : 231.2 [M+H]⁺.

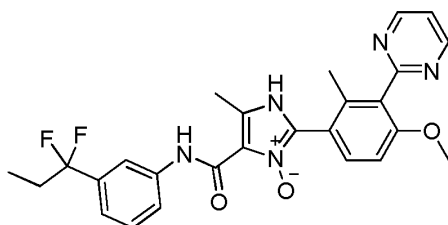
[00344] **Step 5: Synthesis of 4-methoxy-2-methyl-3-pyrimidin-2-yl-benzaldehyde (118-E)**



- [00345] To a solution of **118-D** (30.0 mg, 130 μ mol, 1.0 *eq*) in dichloroethane (1 mL) was added manganese dioxide (113 mg, 1.30 mmol, 10 *eq*). The mixture was stirred at 20 °C for 12 h. The suspension was filtered and the filtrate was concentrated to give 30 mg (crude) of **118-E** as a yellow solid.

[00346] **LCMS:** (ESI) m/z : 229.1 [M+H]⁺.

- [00347] **Step 6: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-2-methyl-3-(pyrimidin-2-yl)phenyl)-5-methyl-1H-imidazole 3-oxide (118)**
- 20

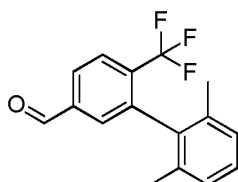


[00348] **118** was obtained *via* general procedure from **103-G** and **118-E**.

[00349] **LCMS:** (ESI) m/z : 494.1 $[M+H]^+$. **1H NMR** (400Hz, DMSO- d_6) δ : 13.80 (s, 1H), 13.30 (s, 1H), 8.94 (d, J = 4.8 Hz, 2H), 7.89 (s, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.51 (t, J = 5.2 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.23-7.19 (m, 1H), 7.18-7.14 (m, 1H), 3.73 (s, 3H), 2.58 (s, 3H), 2.25-2.14 (m, 2H), 1.91 (s, 3H), 0.91 (t, J = 7.6 Hz, 3H).

5 Synthesis of 121

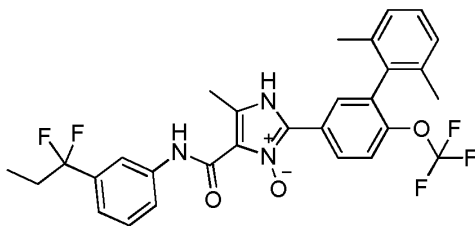
[00350] **Step 1: Synthesis of 3-(2,6-dimethylphenyl)-4-(trifluoromethyl)benzaldehyde (121-A)**



[00351] A mixture of 3-bromo-4-(trifluoromethyl)benzaldehyde (200 mg, 796 μ mol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (179 mg, 1.20 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (92.0 mg, 79.6 μ mol, 0.10 *eq*), potassium phosphate (338 mg, 1.59 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 150 mg (68% yield) of **121-A** as colorless oil.

[00352] **1H NMR** (400Hz, $CDCl_3-d$) δ : 10.12 (s, 1H), 8.01-7.97 (m, 2H), 7.72 (s, 1H), 7.27-7.22 (m, 1H), 7.12 (d, J = 8.0 Hz, 2H), 1.95 (s, 6H).

[00353] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(2',6'-dimethyl-6-(trifluoromethoxy)-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (121)**

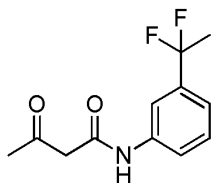


[00354] **121** was obtained *via* general procedure from **103-G** and **121-A**.

[00355] **LCMS:** (ESI) m/z : 544.1 $[M+H]^+$. **1H NMR** (400Hz, DMSO- d_6) δ : 13.36 (brs, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.27-7.16 (m, 4H), 2.59 (s, 3H), 2.26-2.16 (m, 2H), 1.93 (s, 6H), 0.91 (t, J = 7.2 Hz, 3H).

Synthesis of 120

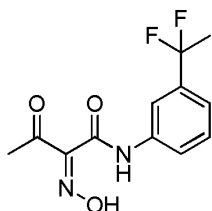
[00356] **Step 1: Synthesis of N-(3-(1,1-difluoroethyl)phenyl)-3-oxobutanamide (120-A)**



[00357] To a mixture of 3-(1,1-difluoroethyl)aniline (6.23 g, 39.7 mmol, 1.0 *eq*) in dichloromethane (50 mL) was added 4-methyleneoxetan-2-one (5.00 g, 59.5 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 3 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was
 5 purified by column chromatography on silica gel (petroleum ether/ethyl acetate, from 5/1 to 4/1) to give 9.60 g (96% yield) of **120-A** as a brown solid.

[00358] LCMS: (ESI) *m/z*: 242.5 [M+H]⁺.

[00359] **Step 2: Synthesis of (Z)-N-(3-(1,1-difluoroethyl)phenyl)-2-(hydroxyimino)-3-oxobutanamide (120-B)**



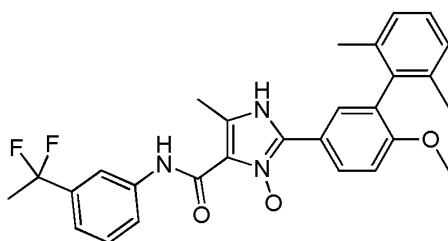
10

[00360] To a 50 mL round-bottom flask equipped with a magnetic stir bar was added **120-A** (1.00 g, 3.98 mmol, 1.0 *eq*) followed by the addition of acetic acid (10 mL). The solution was cooled to 0 °C. Then a solution of sodium nitrite (412 mg, 5.97 mmol, 1.5 *eq*) in water (2 mL) was added dropwise. The mixture was allowed to warm to 25 °C and stir for 12 h. The mixture was diluted by water (30 mL) and
 15 extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 0.960 g (75% yield) of **120-B** as a yellow oil.

[00361] LCMS: (ESI) *m/z*: 271.1 [M+H]⁺.

[00362] **Step 3: Synthesis of 4-((3-(1,1-difluoroethyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (120)**

20

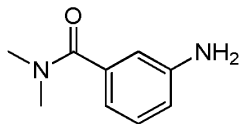


[00363] **120** was obtained *via* general procedure from **102-A** and **120-B**.

[00364] **LCMS:** (ESI) m/z : 492.2 $[M+H]^+$. **¹H NMR** (400Hz, MeOD- d_4) δ : 8.34 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.32-7.30 (m, 2H), 7.17-7.08 (m, 3H), 3.84 (s, 3H), 2.64 (s, 3H), 2.01 (s, 6H), 1.93 (t, J = 18.4 Hz, 3H).

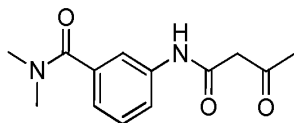
Synthesis of 119

5 [00365] Step 1: Synthesis of 3-amino-*N,N*-dimethylbenzamide (119-A)



[00366] To a solution of *N*-methylmethanamine (1.01 g, 12.4 mmol, 2.0 *eq*, hydrochloric acid) in dichloromethane (5 mL) was added *N,N*-diisopropylethylamine (2.40 g, 18.5 mmol, 3.2 mL, 3.0 *eq*). Then 3-aminobenzoic acid (850 mg, 6.20 mmol, 1.0 *eq*) and 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium (3.54 g, 9.30 mmol, 1.5 *eq*) were added into the solution and the mixture
10 was stirred at 25 °C for 1 h. The solution was poured into water (50 mL), extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give 1.00 g (98 % yield) of **119-A** as a gray oil.

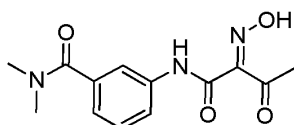
15 [00367] Step 2: Synthesis of *N,N*-dimethyl-3-(3-oxobutanamido)benzamide (119-B)



[00368] **119-B** was obtained *via* general procedure from **119-A**

[00369] **LCMS:** (ESI) m/z : 249.2 $[M+H]^+$

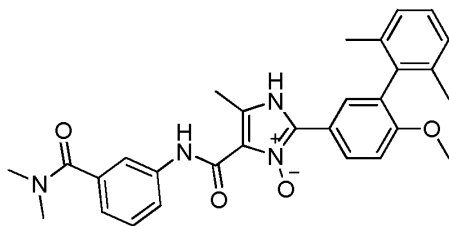
20 [00370] Step 3: Synthesis of 3-[(2*E*)-2-hydroxyimino-3-oxo-butanoyl]amino-*N,N*-dimethylbenzamide (119-C)



[00371] **119-C** was obtained *via* general procedure from **119-B**.

[00372] **LCMS:** (ESI) m/z : 278.2 $[M+H]^+$

25 [00373] Step 4: Synthesis of 4-((3-(dimethylcarbamoyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (119)

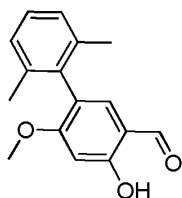


[00374] **119** was obtained *via* general procedure from **102-A** and **119-C**.

[00375] **LCMS**: (ESI) m/z : 499.2 $[M+H]^+$. **1H NMR** (400Hz, DMSO- d_6) δ : 13.59 (brs, 1H), 13.16 (brs, 1H), 8.52 (d, $J = 2.4$ Hz, 1H), 8.12 (d, $J = 2.0$ Hz, 1H), 7.82 (s, 1H), 7.61 (d, $J = 9.2$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 7.20-7.08 (m, 4H), 3.79 (s, 3H), 2.98-2.92 (m, 6H), 2.58 (s, 3H), 1.96 (s, 6H).

Synthesis of 123

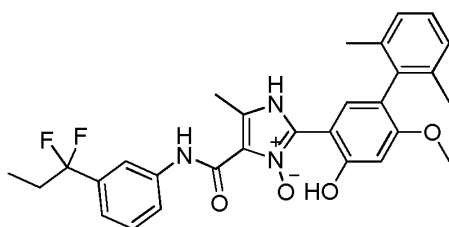
[00376] **Step 1: Synthesis of 5-(2,6-dimethylphenyl)-2-hydroxy-4-methoxy-benzaldehyde (123-A)**



[00377] A mixture of 5-bromo-2-hydroxy-4-methoxy-benzaldehyde (182 mg, 796 μ mol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (179 mg, 1.20 mmol, 1.5 *eq*), tetrakis[triphenylphosphine]palladium (92.0 mg, 79.6 μ mol, 0.10 *eq*), potassium phosphate (338 mg, 1.59 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. Then the reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 140 mg (65% yield) of **123-A** as colorless oil.

[00378] **LCMS**: (ESI) m/z : 257.1 $[M+H]^+$.

[00379] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbonyl)-2-(4-hydroxy-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (123)**



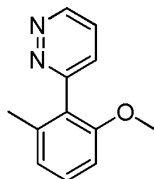
[00380] **123** was obtained *via* general procedure from **123-A** and **103-G**.

[00381] **LCMS**: (ESI) m/z : 522.2 $[M+H]^+$.

[00382] **¹H NMR** (400Hz, DMSO- d_6) δ : 13.46 (brs, 1H), 13.15 (brs, 1H), 12.10 (s, 1H), 7.96 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 7.16-7.08 (m, 3H), 6.69 (s, 1H), 3.7 4 (s, 3H), 2.57 (s, 3H), 2.29-2.15 (m, 2H), 1.99 (s, 6H), 0.93 (t, J = 7.2 Hz, 3H).

Synthesis of 122

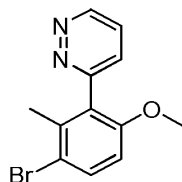
[00383] **Step 1: Synthesis of 3-(2-methoxy-6-methylphenyl)pyridazine (122-A)**



[00384] A mixture of **144-A** (200 mg, 1.20 mmol, 1.1 *eq*), 3-bromopyridazine (172 mg, 1.10 mmol, 1.0 *eq*), tetrakis(triphenylphosphine)palladium (127 mg, 110 μ mol, 0.10 *eq*), sodium carbonate (232 mg, 2.19 mmol, 2.0 *eq*) and water (0.5 mL) in 1,2-dimethoxyethane (2.5 mL) was stirred at 100 °C for 12 hr under nitrogen atmosphere. The mixture was concentrated in vacuum to give the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 140 mg (59% yield) of **122-A** as a yellow solid.

[00385] **LCMS**: (ESI) m/z : 201.2 $[M+H]^+$

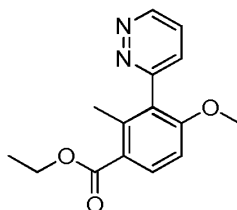
[00386] **Step 2: Synthesis of 3-(3-bromo-6-methoxy-2-methylphenyl)pyridazine(122-B).**



[00387] To a solution of **122-A** (140 mg, 650 μ mol, 1.0 *eq*) in acetonitrile (2 mL) was added 1-bromopyrrolidine-2,5-dione (127 mg, 715 μ mol, 1.1 *eq*). The mixture was stirred at 25 °C for 2 h. The mixture was poured into saturated sodium sulfite (20 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layer was washed brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give 180 mg (94% yield) of **122-B** as a yellow solid.

[00388] **LCMS**: (ESI) m/z : 280.2 $[M+H]^+$.

[00389] **Step 3: Synthesis of ethyl 4-methoxy-2-methyl-3-(pyridazin-3-yl)benzoate (122-C).**

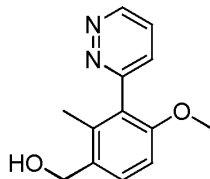


[00390] A mixture of **122-B** (180 mg, 613 μmol , 1.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (672 mg, 918 μmol , 1.5 *eq*) and triethylamine (186 mg, 1.84 mmol, 0.3 mL, 3.0 *eq*) in ethanol (5 mL) was stirred at 70 °C for 36 h under carbonic oxide atmosphere (50 Psi). The mixture was concentrated in vacuum to give the residue. The residue

5 was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 80 mg (48% yield) of **122-C** as a yellow liquid.

[00391] LCMS: (ESI) m/z : 273.1 $[\text{M}+\text{H}]^+$.

[00392] **Step 4: Synthesis of (4-methoxy-2-methyl-3-pyridazin-3-yl-phenyl)methanol (122-D)**

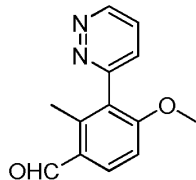


10 [00393] To a solution of **122-C** (80.0 mg, 275 μmol , 1.0 *eq*) in tetrahydrofuran (2 mL) was added diisobutyl aluminum hydride (1 M, 1.2 mL, 4.0 *eq*) at 0°C. The reaction was stirred at 25 °C for 12 h. The reaction was quenched by adding saturated ammonium chloride (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL x 2). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 60.0 mg

15 (90% yield) of **122-D** as a yellow solid.

[00394] LCMS: (ESI) m/z : 231.2 $[\text{M}+\text{H}]^+$.

[00395] **Step 5: Synthesis of 4-methoxy-2-methyl-3-pyridazin-3-yl-benzaldehyde (122-E)**

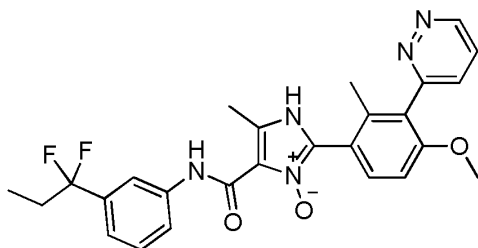


[00396] To a solution of **122-D** (30.0 mg, 130 μmol , 1.0 *eq*) in dichloroethane (1 mL) was added manganese dioxide (113 mg, 1.30 mmol, 10 *eq*). The mixture was stirred at 20 °C for 12 h. The suspension was filtered and the filtrate was concentrated to give 30 mg (crude) of **122-E** as a yellow solid.

20

[00397] LCMS: (ESI) m/z : 229.1 $[\text{M}+\text{H}]^+$. **Step 6: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-2-methyl-3-(pyridazin-3-yl)phenyl)-5-methyl-1H-imidazole 3-oxide (122)**

25

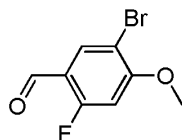


[00398] **122** was obtained *via* general procedure from **122-E** and **103-G**.

[00399] **LCMS**: (ESI) m/z : 494.1 $[M+H]^+$. **1H NMR** (400Hz, DMSO- d_6) δ : 13.68 (s, 1H), 9.25 (d, J = 6.6 Hz, 1H), 7.89 (s, 1H), 7.80 (d, J = 13.4 Hz, 1H), 7.68 (s, 1H), 7.67-7.63 (m, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 2.59 (s, 3H), 2.26 (s, 1H), 1.97 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H).

Synthesis of 125

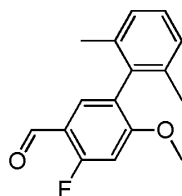
[00400] **Step 1: 5-bromo-2-fluoro-4-methoxybenzaldehyde (125-A)**



[00401] To a solution of potassium bromide (77.2 g, 649 mmol, 5.0 *eq*) and bromine (41.5 g, 260 mmol, 13 mL, 2.0 *eq*) in water (100 mL) was added 2-fluoro-4-methoxy-benzaldehyde (20.0 g, 130 mmol, 1.0 *eq*) slowly under 0 °C. The mixture was stirred at 20 °C for 3 hr. Then the suspension was filtered, and filter-cake was dried in vacuum to give 30.0 g (99% yield) of **125-A** as a yellow solid.

[00402] **1H NMR** (400 MHz, $CDCl_3-d$) δ : 10.16 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 11.6 Hz, 1H), 3.98 (s, 3H)

[00403] **Step 2: 4-fluoro-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (125-B)**

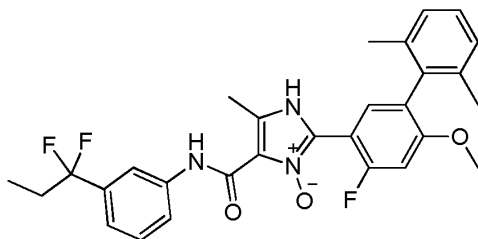


[00404] A mixture of **125-A** (15.0 g, 64.3 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (11.6 g, 77.2 mmol, 1.2 *eq*), tri(dibenzylideneacetone)dipalladium(0) (5.89 g, 6.44 mmol, 0.10 *eq*), dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl]phosphane (5.29 g, 12.9 mmol, 0.20 *eq*) and potassium phosphate (20.5 g, 96.6 mmol, 1.5 *eq*) in toluene (150 mL) and water (15 mL) was stirred at 100 °C for 12 hr under nitrogen atmosphere. The mixture was poured into saturated ammonium chloride (200 mL), extracted with ethyl acetate (250 mL $\times$ 3). The combined organic layer was washed with brine (150 mL), dried

over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (silica gel, Petroleum ether/Ethyl acetate from 1/0 to 30/1) to give 10.5 g (63% yield) of **125-B** as a yellow solid.

[00405] ¹H NMR (400 MHz, CDCl₃-d) δ: 10.28 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.23-7.18 (m, 1H),
5 7.14-7.10 (m, 2H), 6.77 (d, *J* = 12.4 Hz, 1H), 3.83 (s, 3H), 1.99 (s, 6H).

[00406] **Step 3: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-fluoro-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (125)**



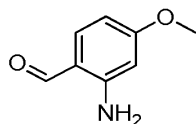
[00407] **125** was obtained *via* general procedure from **103-G** and **125-B**

10 [00408] **LCMS**: (ESI) *m/z*: 524.3 [M+H]⁺.

[00409] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 13.55 (s, 1H), 13.09 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 13.2 Hz, 1H), 7.22-7.16 (m, 2H), 7.13-7.10 (m, 2H), 3.81 (s, 3H), 2.61 (s, 3H), 2.25-2.14 (m, 2H), 1.97 (s, 6H), 0.90 (t, *J* = 7.6 Hz, 3H).

Synthesis of 124

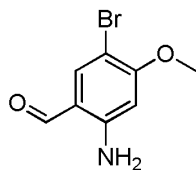
15 [00410] **Step 1: Synthesis of 2-amino-4-methoxy-benzaldehyde (124-A)**



[00411] To a solution of 4-methoxy-2-nitro-benzaldehyde (500 mg, 2.76 mmol, 1.0 *eq*) in ethanol (5 mL) and water (1 mL) were added iron powder (771 mg, 13.8 mmol, 5.0 *eq*) and ammonium chloride (738 mg, 13.8 mmol, 5.0 *eq*). The suspension was stirred at 60 °C for 1 h. The suspension was filtered
20 and concentrated under reduced pressure to give 190 mg (crude) of **124-A** as a light gray oil.

[00412] **LCMS**: (ESI) *m/z*: 152.1 [M+H]⁺.

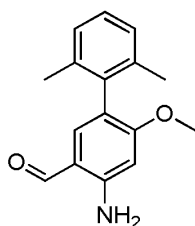
[00413] **Step 2: Synthesis of 2-amino-5-bromo-4-methoxybenzaldehyde (124-B)**



[00414] To a solution of **124-A** (300 mg, 1.98 mmol, 1.0 *eq*) in dichloromethane (5 mL) was added 1-bromopyrrolidine-2,5-dione (318 mg, 1.79 mmol, 0.90 *eq*). The solution was stirred at 25 °C for 12 h. Then the suspension was poured into water (10 mL), extracted with dichloromethane (10 mL x 3). The combined organic layer was washed with saturated sodium bicarbonate (10 mL), brine (10 mL), dried with anhydrous sodium sulfate, filtered and concentrated to give a residue pressure to give 200 mg (38% yield) of **124-B** as a light gray oil.

[00415] **LCMS**: (ESI) *m/z*: 232.0 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃-*d*) δ : 9.66 (s, 1H), 7.59 (s, 1H), 6.30 (s, 2H), 6.10 (s, 1H), 3.90 (s, 3H).

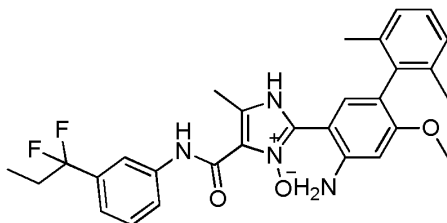
[00416] **Step 3: Synthesis of 4-amino-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (124-C)**



[00417] **124** was obtained *via* similar procedure of **102-A** from **124-B** and (2,6-dimethylphenyl)boronic acid.

[00418] **LCMS**: (ESI) *m/z*: 256.1 [M+H]⁺.

[00419] **Step 4: Synthesis of (2-[2-amino-5-(2,6-dimethylphenyl)-4-methoxy-phenyl]-N-[3-(1,1-difluoropropyl)phenyl]-5-methyl-3-oxido-1*H*-imidazol-3-ium-4-carboxamide (124)**

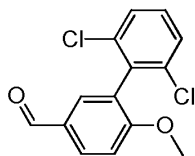


[00420] **124** was obtained *via* general procedure from **124-C** and **103-G**.

[00421] **LCMS**: (ESI) *m/z*: 521.3 [M+H]⁺. **¹H NMR** (400Hz, DMSO-*d*₆) δ : 13.1 (s, 1H), 7.94 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.14-7.06 (m, 3H), 6.97 (s, 1H), 6.71 (s, 1H), 3.71 (s, 3H), 2.56 (s, 3H), 2.15-2.07 (m, 2H), 1.99 (s, 6H), 0.92 (t, *J* = 7.6 Hz, 3H).

Synthesis of 126

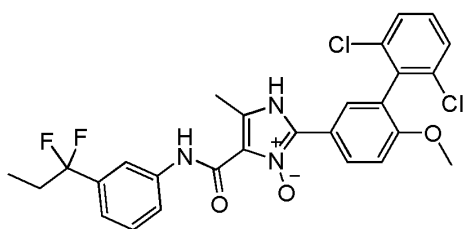
[00422] **Step 1: Synthesis of 2',6'-dichloro-6-methoxy-[1,1'-biphenyl]-3-carbaldehyde (126-A)**



[00423] A mixture of 3-bromo-4-methoxybenzaldehyde (169 mg, 796 μmol , 1.0 *eq*), (2,6-dichlorophenyl)boronic acid (228 mg, 1.20 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (92.0 mg, 79.6 μmol , 0.10 *eq*), potassium phosphate (338 mg, 1.59 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 130 mg (58% yield) of **126-A** as colorless oil

[00424] **LCMS:** (ESI) m/z : 281.0 $[\text{M}+\text{H}]^+$.

[00425] **Step 2: Synthesis of 2-(2',6'-dichloro-6-methoxy-[1,1'-biphenyl]-3-yl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (126)**

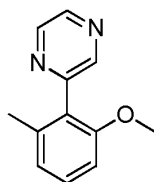


[00426] **126** was obtained *via* general procedure from **126-A** and **103-G**.

[00427] **LCMS:** (ESI) m/z : 546.3 $[\text{M}+\text{H}]^+$. **^1H NMR** (400Hz, $\text{MeOD}-d_4$) δ : 8.44 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 8.03 (d, $J = 2.4$ Hz, 1H), 7.92 (s, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.38-7.32 (m, 2H), 7.24 (d, $J = 7.6$ Hz, 1H), 3.87 (s, 3H), 2.66 (s, 3H), 2.25-2.03 (m, 2H), 0.98 (t, $J = 7.2$ Hz, 3H).

[00428] **Synthesis of 127**

[00428] **Step 1: Synthesis of 2-(2-methoxy-6-methyl-phenyl)pyrazine (127-A)**

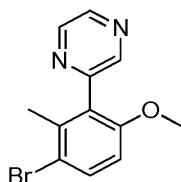


[00429] A mixture of **144-A** (200 mg, 1.20 mmol, 1.1 *eq*), 2-bromopyrazine (212 mg, 1.10 mmol, 1.0 *eq*, hydrochloride), tetrakis(triphenylphosphine)palladium (127 mg, 110 μmol , 0.10 *eq*), sodium

carbonate (232 mg, 2.19 mmol, 2.0 *eq*) and water (0.5 mL) in 1,2-dimethoxyethane (2.5 mL) was stirred at 100 °C for 12 hr under nitrogen atmosphere. The mixture was concentrated in vacuum to give the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 120 mg (50% yield) of **127-A** as a yellow solid.

5 [00430] **LCMS:** (ESI) *m/z*: 201.2 [M+H]⁺.

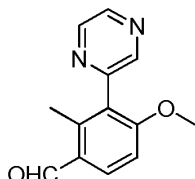
[00431] **Step 2: Synthesis of 2-(3-bromo-6-methoxy-2-methyl-phenyl)pyrazine (127-B)**



[00432] To a solution of **127-A** (140 mg, 650 umol, 1.0 *eq*) in acetonitrile (2 mL) was added 1-bromopyrrolidine-2,5-dione (127 mg, 715 umol, 1.1 *eq*). The mixture was stirred at 25 °C for 2 h. The mixture was poured into saturated sodium sulfite (20 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give 180 mg (94% yield) of **127-B** as a yellow solid

[00433] **LCMS:** (ESI) *m/z*: 281.0 [M+H]⁺.

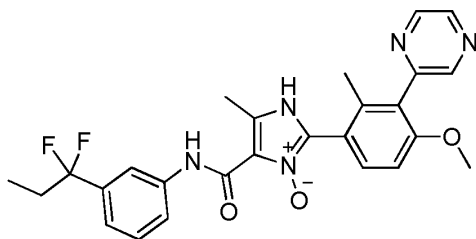
[00434] **Step 3: Synthesis of 4-methoxy-2-methyl-3-pyrazin-2-yl-benzaldehyde (127-C).**



15 [00435] To a solution of **127-B** (250 mg, 797 umol, 1 *eq*) in THF (5 mL) was added dropwise *n*-butyllithium (2.5 M, 478 uL, 1.5 *eq*) at -78°C under nitrogen. After stirred for 30 min, *N,N*-dimethylformamide (87.4 mg, 1.20 mmol, 1.5 *eq*) was added dropwise. After stirring for 30 min at -78 °C, the reaction was warmed to 25°C and stirred for 1 hr. The reaction was quenched by adding hydrochloric acid (1 M, 1 mL). The aqueous phase was extracted with ethyl acetate (10 mL × 2). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/1) to give 100 mg (55% yield) of **127-C** as a yellow solid.

20 [00436] **LCMS:** (ESI) *m/z*: 229.2 [M+H]⁺.

[00437] **Step 4: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-2-methyl-3-(pyrazin-2-yl)phenyl)-5-methyl-1*H*-imidazole 3-oxide (127)**

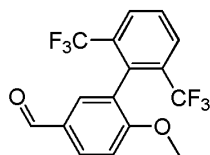


[00438] **122** was obtained *via* general procedure from **127-C** and **103-G**.

[00439] **LCMS**: (ESI) m/z : 494.1 $[M+H]^+$. **¹H NMR** (400Hz, DMSO- d_6) δ : 13.70 (s, 1H), 8.78 (d, J = 4.2 Hz, 1H), 8.64 (d, J = 4.0 Hz, 2H), 7.89 (s, 1H), 7.67-7.61 (m, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.24-7.18 (m, 2H), 3.77 (s, 3H), 2.58 (s, 3H), 2.26-2.13 (m, 2H), 1.99 (s, 3H), 0.91 (t, J = 7.6 Hz, 3H).

Synthesis of 128

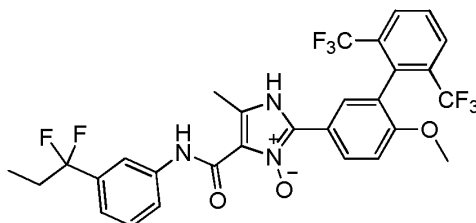
[00440] **Step 1: Synthesis of 6-methoxy-2',6'-bis(trifluoromethyl)-[1,1'-biphenyl]-3-carbaldehyde (128-A)**



[00441] A mixture of (5-formyl-2-methoxyphenyl)boronic acid (150 mg, 796 μ mol, 1.0 *eq*), 2-bromo-1,3-bis(trifluoromethyl)benzene (350 mg, 1.20 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (92.0 mg, 79.6 μ mol, 0.10 *eq*), potassium phosphate (338 mg, 1.59 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 160 mg (58% yield) of **128-A** as colorless oil.

[00442] **LCMS**: (ESI) m/z : 349.0 $[M+H]^+$.

[00443] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (128)**

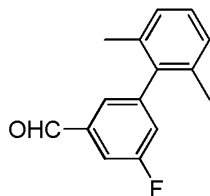


[00444] **128** was obtained *via* general procedure from **128-A** and **103-G**.

[00445] **LCMS**: (ESI) m/z : 614.2 $[M+H]^+$. **1H NMR** (400MHz, DMSO- d_6) δ : 13.6 (s, 1H), 13.34 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.48 (s, 1H), 8.19 (d, J = 8.0 Hz, 2H), 7.91-7.89 (m, 2H), 7.69 (s, 1H), 7.44 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 2.60 (s, 3H), 2.27-2.13 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

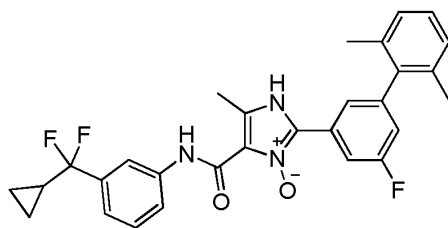
Synthesis of 129

[00446] **Step 1: Synthesis of 5-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (129-A)**



[00447] A mixture of 3-bromo-5-fluorobenzaldehyde (160 mg, 796 μ mol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (180 mg, 1.20 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (92.0 mg, 79.6 μ mol, 0.10 *eq*), potassium phosphate (338 mg, 1.59 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 170 mg (90% yield) of **129-A** as colorless oil.

[00448] **Step 2: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(5-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (129)**

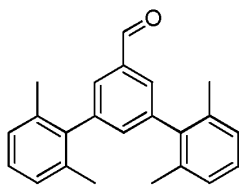


[00449] **129** was obtained *via* general procedure from **129-A** and **161-E**.

[00450] **LCMS**: (ESI) m/z : 506.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.26-8.22 (m, 1H), 7.99 (s, 1H), 7.83 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.22-7.18 (m, 1H), 7.15-7.10 (m, 3H), 2.68 (s, 3H), 2.08 (s, 6H), 1.65-1.56 (m, 1H), 0.75-0.68 (m, 4H).

Synthesis of 132

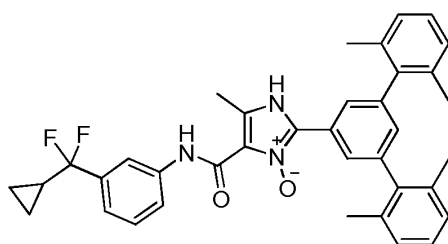
[00451] **Step 1: Synthesis of 3,5-bis(2,6-dimethylphenyl)benzaldehyde (132-A)**



[00452] **132-A** was obtained *via* similar procedure of **102-A** from (2,6-dimethylphenyl)boronic acid and 3,5-dibromobenzaldehyde.

[00453] **LCMS**: (ESI) m/z : 315.1 $[M+H]^+$.

- 5 [00454] **Step 2: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-2-(2,2'',6,6''-tetramethyl-[1,1':3,1''-terphenyl]-5'-yl)-1H-imidazole 3-oxide (132)**

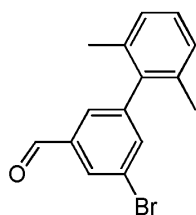


[00455] **132** was obtained *via* general procedure from **132-A** and **161-E**.

- [00456] **LCMS**: (ESI) m/z : 592.2 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 8.11 (d, J = 1.6 Hz, 2H),
 10 7.99 (s, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.20-7.12 (m, 6H), 7.06 (s, 1H), 2.67 (s, 3H), 2.12 (s, 12H), 1.65-1.62 (m, 1H), 0.73-0.66 (m, 4H).

Synthesis of 133

- [00457] **Step 1: Synthesis of 5-bromo-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (133-A)**

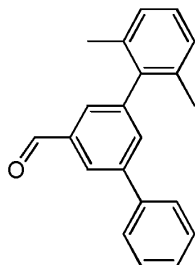


- 15 [00458] A mixture of 3,5-dibromobenzaldehyde (200 mg, 796 μ mol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (180 mg, 1.20 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (92.0 mg, 79.6 μ mol, 0.10 *eq*), potassium phosphate (338 mg, 1.59 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and
 20 aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 160 mg

(70% yield) of **133-A** as colorless oil.

[00459] ¹H NMR (400 MHz, CDCl₃-d) δ: 10.00 (s, 1H), 8.02 (t, *J* = 1.6 Hz, 1H), 7.63 (t, *J* = 1.2 Hz, 1H), 7.60 (t, *J* = 1.6 Hz, 1H), 7.20 (t, *J* = 6.8 Hz, 1H), 7.15-7.13 (m, 2H), 2.04 (s, 6H).

[00460] **Step 2: Synthesis of 2,6-dimethyl-[1,1':3',1''-terphenyl]-5'-carbaldehyde (133-B)**

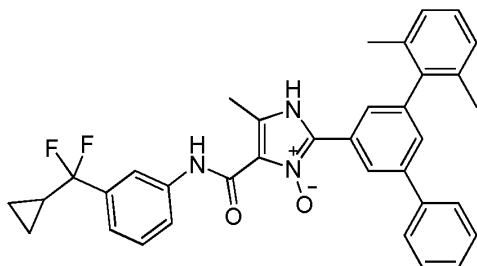


5

[00461] **133-B** was obtained *via* similar procedure of **133-A** from **133-A** and phenylboronic acid.

[00462] ¹H NMR (400 MHz, CDCl₃-d) δ: 10.14 (s, 1H), 8.13 (t, *J* = 1.6 Hz, 1H), 7.71 (t, *J* = 1.6 Hz, 1H), 7.69-7.67 (m, 3H), 7.51-7.47 (m, 2H), 7.44-7.39 (m, 1H), 7.25-7.21 (m, 1H), 7.17-7.15 (m, 2H), 2.09 (s, 6H).

10 [00463] **Step 3: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(2,6-dimethyl-[1,1':3',1''-terphenyl]-5'-yl)-5-methyl-1*H*-imidazole 3-oxide (133)**

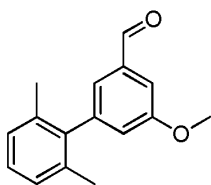


[00464] **133** was obtained *via* general procedure from **133-B** and **161-E**.

15 [00465] **LCMS**: (ESI) *m/z*: 564.3 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ: 8.66 (t, *J* = 1.6 Hz, 1H), 8.05 (t, *J* = 1.6 Hz, 1H), 8.00 (s, 1H), 7.78-7.75 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 1.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.46-7.39 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.22-7.18 (m, 1H), 7.16-7.14 (m, 2H), 2.70 (s, 3H), 2.12 (s, 6H), 1.64-1.58 (m, 1H), 0.73-0.69 (m, 4H).

Synthesis of 131

[00466] **Step 1: Synthesis of 3-(2,6-dimethylphenyl)-5-methoxy-benzaldehyde (131-A)**

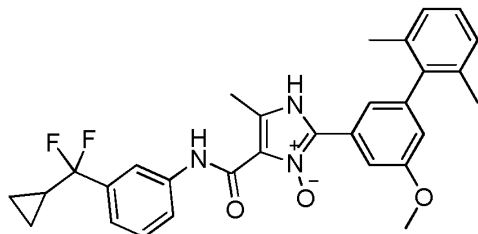


20

[00467] **131-A** was obtained *via* similar procedure of **133-A** from 3-bromo-5-methoxy-benzaldehyde and (2,6-dimethylphenyl)boronic acid.

[00468] **LCMS**: (ESI) m/z : 241.1 $[M+H]^+$.

[00469] **Step 2: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(5-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (131).**

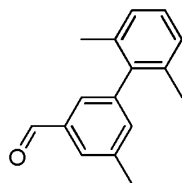


[00470] **131** was obtained *via* general procedure from **131-A** and **161-E**.

[00471] **LCMS**: (ESI) m/z : 518.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.03 (d, J = 3.8 Hz, 1H), 7.98 (s, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.57 (t, J = 1.4 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.20-7.09 (m, 3H), 6.88 (d, J = 3.8 Hz, 1H), 3.93 (s, 3H), 2.67 (s, 3H), 2.07 (s, 6H), 1.66-1.56 (m, 1H), 0.75-0.66 (m, 4H).

Synthesis of 130

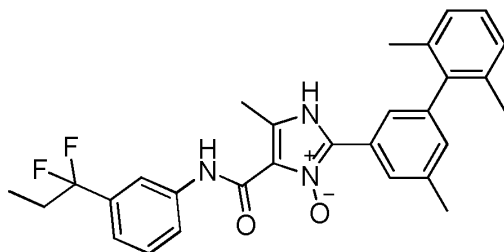
[00472] **Step 1: Synthesis of 3-(2,6-dimethylphenyl)-5-methyl-benzaldehyde (130-A)**



[00473] A mixture of 3-bromo-5-methyl-benzaldehyde (500 mg, 2.51 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (452 mg, 3.01 mmol, 1.2 *eq*), tetrakis(triphenylphosphine)platinum (871 mg, 754 μ mol, 0.30 *eq*), potassium phosphate (1.07 g, 5.02 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (10 mL) and water (5 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 400 mg (68% yield) of **130-A** as a colorless oil.

[00474] **LCMS**: (ESI) m/z : 225.2 $[M+H]^+$.

[00475] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-2-(2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-1H-imidazole 3-oxide (130)**

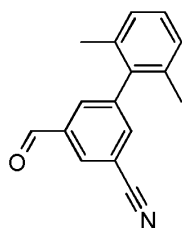


[00476] **130** was obtained *via* general procedure from **130-A** and **103-G**.

[00477] **LCMS**: (ESI) m/z : 502.3 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ : 13.6 (s, 1H), 8.33 (s, 1H), 8.01 (d, J = 6.8 Hz, 2H), 7.70 (d, J = 9.2 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H),
 5 7.23-7.11 (m, 4H), 2.60 (s, 3H), 2.45 (s, 3H), 2.01 (s, 6H), 1.78-1.66 (m, 1H), 0.75-0.56 (m, 4H).

Synthesis of 135

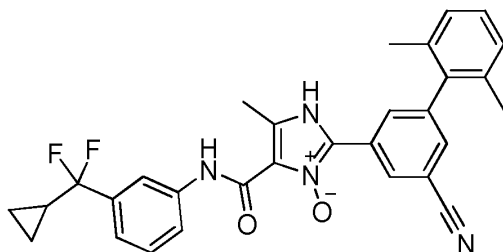
[00478] **Step 1: Synthesis of cyclopropyl(phenyl)methanone (135-A)**



[00479] To a solution of **161-F** (500 mg, 1.73 mmol, 1.0 *eq*) and zinc cyanide (450 mg, 3.83 mmol, 2.2
 10 *eq*) in *N,N*-dimethylformamide (5 mL) was added tetrakis[triphenylphosphine]palladium (300 mg, 259
 umol, 0.15 *eq*). The reaction was degassed and purged with nitrogen. Then it was stirred at 120 °C for
 2 h under nitrogen atmosphere. To the mixture was added water (50 mL) and the aqueous was extracted
 with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (60 mL), dried over
 anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue
 15 was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 170 mg
 (42% yield) of **135-A** as a yellow solid.

[00480] **1H NMR** (400 MHz, CDCl₃-*d*) δ : 10.1 (s, 1H), 8.17 (t, J = 1.6 Hz, 1H), 7.93 (t, J = 1.6 Hz, 1H),
 7.73 (t, J = 1.6 Hz, 1H), 7.26-7.20 (m, 1H), 7.18-7.14 (m, 2H), 2.02 (s, 6H).

[00481] **Step 2: Synthesis of 2-(5-cyano-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1*H*-imidazole 3-oxide (135)**
 20

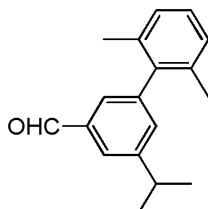


[00482] **135** was obtained *via* general procedure from **135-A** and **161-E**

[00483] **LCMS**: (ESI) m/z : 513.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.79 (t, $J = 1.6$ Hz, 1H), 8.35 (t, $J = 1.6$ Hz, 1H), 8.00 (s, 1H), 7.71-7.67 (m, 2H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 7.6$ Hz, 1H), 7.24-7.20 (m, 1H), 7.18- 7.14 (m, 2H), 2.68 (s, 3H), 2.07 (s, 6H), 1.65-1.55 (m, 1H), 0.74-0.68 (m, 4H).

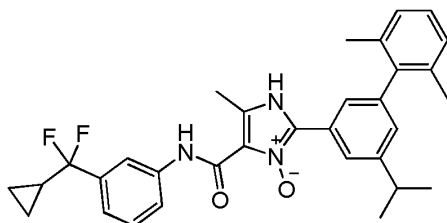
Synthesis of 134

[00484] **Step 1: Synthesis of 5-isopropyl-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (134-A)**



[00485] A mixture of 3-bromo-5-isopropylbenzaldehyde (200 mg, 828 μ mol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (148 mg, 991 μ mol, 1.2 *eq*), tetrakis(triphenylphosphine)palladium (260 mg, 754 μ mol, 0.30 *eq*), potassium phosphate (349 g, 1.65 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (10 mL) and water (5 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 3). The organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 170 mg (85% yield) of **134-A** as a colorless oil.

[00486] **Step 2: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(5-isopropyl-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (134)**

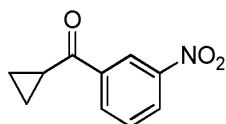


[00487] **134** was obtained *via* general procedure from **134-A** and **161-E**.

[00488] **LCMS:** (ESI) m/z : 530.3 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.23 (t, J = 1.6 Hz, 1H), 7.99 (s, 1H), 7.87 (t, J = 1.6 Hz, 1H), 7.74-7.68 (m, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.22-7.19 (m, 1H), 7.18-7.10 (m, 3H), 3.14-3.02 (m, 1H), 2.68 (s, 3H), 2.05 (s, 6H), 1.65-1.56 (m, 1H), 1.37 (d, J = 6.8 Hz, 6H), 0.74-0.67 (m, 4H).

5 **Synthesis of 161**

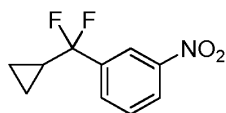
[00489] **Step 1: Synthesis of cyclopropyl(phenyl)methanone (161-A)**



[00490] To a solution of cyclopropyl(phenyl)methanone (20.0 g, 137 mmol, 1.0 *eq*) in sulfuric acid (100 mL) was added a solution of fuming nitric acid (21.0 g, 333 mmol, 2.4 *eq*) in sulfuric acid (27.6 g, 281 mmol, 2.1 *eq*) at -10 °C. The reaction was stirred at 0 °C for 1 h. Then the reaction mixture was added dropwise into the ice water (200 mL) and quenched with saturated aqueous sodium bicarbonate solution (500 mL). The suspension was extracted with ethyl acetate (300 mL x 3). The combined organic layer was washed with brine (500 mL), filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 20.0 g (38% yield) of **161-A** as a white solid.

[00491] **1H NMR** (400 MHz, MeOD- d_4) δ : 8.83 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 7.2 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 2.73-2.67 (m, 1H), 1.31 (d, J = 3.2 Hz, 2H), 1.18-1.13 (m, 2H).

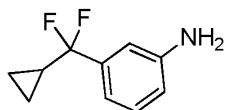
[00492] **Step 2: Synthesis of 1-[cyclopropyl(difluoro)methyl]-3-nitro-benzene (161-B)**



[00493] A mixture of **161-B** (6.00 g, 31.4 mmol, 1.0 *eq*) and bis(2-methoxyethyl)aminosulfur trifluoride (121 g, 548 mmol, 120 mL, 17 *eq*) was stirred at 70 °C for 48 h. The mixture was quenched with ice saturated aqueous sodium bicarbonate solution (300 mL) and the aqueous layer mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layer was washed with brine (100 mL) filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 13 g (61% yield) of **161-B** as a yellow gum.

[00494] **1H NMR** (400 MHz, MeOD- d_4) δ : 8.33 (s, 1H), 8.23-8.20 (m, 1H), 7.81-7.79 (m, 1H), 7.56 (t, J = 8.0 Hz, 1H), 1.49-1.40 (m, 1H), 0.76-0.72 (m, 2H), 0.69-0.64 (m, 2H).

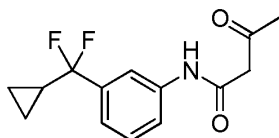
[00495] **Step 3: Synthesis of 3-[cyclopropyl(difluoro)methyl]aniline (161-C)**



[00496] To a solution of **161-B** (6.50 g, 30.5 mmol, 1.0 *eq*) in ethanol (60 mL) and water (30 mL) were added iron powder (6.81 g, 122 mmol, 4.0 *eq*) and ammonium chloride (6.52 g, 122 mmol, 4.0 *eq*). The mixture was stirred at 50 °C for 30 min. The suspension was filtered through a pad of celite. The filter-cake was rinsed with methanol (80 ml) and the filtrate was dried over sodium sulfate, concentrated under reduced pressure to afford a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 10.0 g (90% yield) of **161-C** as a yellow gum.

[00497] **LCMS**: (ESI) *m/z*: 184.3 [M+H]⁺.

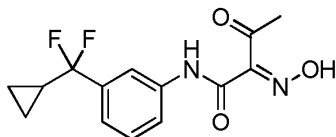
[00498] **Step 4: Synthesis of N-[3-[cyclopropyl(difluoro)methyl]phenyl]-3-oxo-butanamide (161-D)**



[00499] **161-D** was obtained *via* general procedure from **161-C**.

[00500] **LCMS**: (ESI) *m/z*: 268.1 [M+H]⁺.

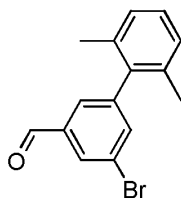
[00501] **Step 5: Synthesis of (2Z)-N-[3-[cyclopropyl(difluoro)methyl]phenyl]-2-hydroxyimino-3-oxo-butanamide (161-E)**



[00502] **161-E** was obtained *via* general procedure from **161-D**.

[00503] **LCMS**: (ESI) *m/z*: 297.2 [M+H]⁺.

[00504] **Step 6: Synthesis of 3-bromo-5-(2,6-dimethylphenyl)benzaldehyde (161-F)**



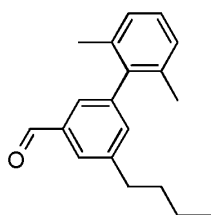
20

[00505] A mixture of 3,5-dibromobenzaldehyde (200 mg, 796 μmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (180 mg, 1.20 mmol, 1.5 *eq*), tetrakis[triphenylphosphine]palladium (92.0

mg, 79.6 μmol , 0.10 *eq*), potassium phosphate (338 mg, 1.59 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 160 mg (70% yield) of **161-F** as colorless oil.

[00506] ¹H NMR (400 MHz, MeOD-*d*₄) δ : 9.97 (s, 1H), 8.06-8.04 (m, 1H), 7.63-7.59 (m, 2H), 7.22-7.13 (m, 3H), 2.00 (s, 6H).

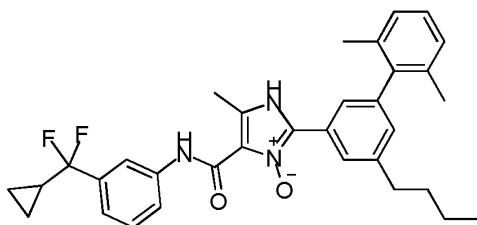
10 [00507] **Step 7: Synthesis of 3-butyl-5-(2,6-dimethylphenyl)benzaldehyde (161-G)**



[00508] To a solution of **161-F** (50.0 mg, 173 μmol , 1.0 *eq*), butylboronic acid (21.2 mg, 207 μmol , 1.2 *eq*), sodium carbonate (36.6 mg, 345 μmol , 2.0 *eq*) in dioxane (2 mL) and water (0.5 mL) was added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (25.3 mg, 34.5 μmol , 0.20 *eq*). The reaction was degassed and purged with nitrogen, and stirred at 100 °C for 12 h. To the mixture was added water (5 mL). The suspension was extracted with ethyl acetate (5 mL x 3). The combined organic layer was washed with brine (6 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 5.00 mg (11% yield) of **161-G** as a yellow gum.

20 [00509] ¹H NMR (400 MHz, CDCl₃-*d*) δ : 10.1 (s, 1H), 7.70 (t, *J* = 1.6 Hz, 1H), 7.50 (t, *J* = 1.6 Hz, 1H), 7.34-7.22 (m, 2H), 7.21-7.12 (m, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.03 (s, 6H), 1.69-1.65 (m, 2H), 1.40-1.35 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H).

[00510] **Step 8: Synthesis of 2-(5-butyl-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1*H*-imidazole 3-oxide (161)**



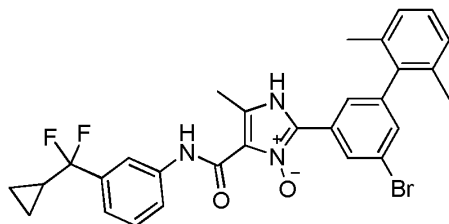
25

[00511] **161** was obtained *via* general procedure from **161-G** and **161-E**

[00512] **LCMS:** (ESI) m/z : 544.3 $[M+H]^+$. **1H NMR** (400 MHz, $CDCl_3-d$) δ : 11.8 (s, 1H), 8.02-7.78 (m, 3H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.42-7.35 (m, 1H), 7.33-7.28 (m, 1H), 7.19-7.13 (m, 2H), 7.11-7.06 (m, 2H), 2.66 (t, $J = 8.0$ Hz, 2H), 2.41 (s, 3H), 1.98 (s, 6H), 1.59 (t, $J = 7.6$ Hz, 2H), 1.52 (s, 1H), 1.35-1.27 (m, 2H), 0.87 (t, $J = 7.2$ Hz, 3H), 0.79-0.74 (m, 2H), 0.67-0.65 (m, 2H).

5 Synthesis of 136

[00513] **Step 1: Synthesis of 2-[3-bromo-5-(2,6-dimethylphenyl)phenyl]-N-[3-(cyclopropyl(difluoro)methyl)phenyl]-5-methyl-3-oxido-1H-imidazol-3-ium-4-carboxamide (136)**

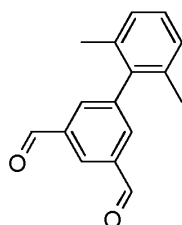


10 [00514] **136** was obtained *via* general procedure from **161-F** and **161-E**.

[00515] **LCMS:** (ESI) m/z : 568.2 $[M+H]^+$. **1H NMR** (400 MHz, $MeOD-d_4$) δ : 8.63 (t, $J = 1.6$ Hz, 1H), 8.04-7.99 (m, 2H), 7.71-7.68 (m, 1H), 7.50 (t, $J = 1.6$ Hz, 1H), 7.46-7.42 (m, 1H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.22-7.18 (m, 1H), 7.15-7.13 (m, 2H), 2.68 (s, 3H), 2.07 (s, 6H), 1.64 (s, 1H), 0.73-0.68 (m, 4H).

Synthesis of 143

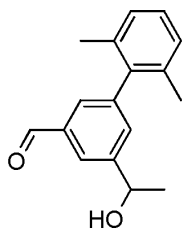
15 [00516] **Step 1: Synthesis of 5-bromobenzene-1,3-dicarbaldehyde (143-A)**



[00517] A mixture of 5-bromobenzene-1,3-dicarbaldehyde (2.00 g, 9.39 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (1.69 g, 11.3 mmol, 1.2 *eq*), tetrakis(triphenylphosphine)palladium (1.63 g, 1.41 mmol, 0.15 *eq*), potassium phosphate (3.99 g, 18.8 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 4/1) to give 1.20 g (54% yield) of **143-A** as a white solid.

[00518] **LCMS:** (ESI) m/z : 239.1 $[M+H]^+$.

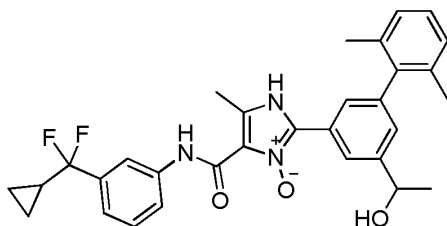
[00519] **Step 2: Synthesis of 5-(2,6-dimethylphenyl)benzene-1,3-dicarbaldehyde (143-B)**



[00520] To a solution of **143-A** (500 mg, 2.10 mmol, 1.0 *eq*) in tetrahydrofuran (20 mL) was added
 5 bromo(methyl)magnesium (3 M, 700 μ L, 1.0 *eq*) dropwise at 0 °C. The reaction was stirred at 0 °C for
 1 h under nitrogen. The reaction mixture was added into hydrochloric acid (1 M, 20 mL) and extracted
 with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over
 anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue
 was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 70.0 mg
 10 (13 % yield) of **143-B** as a colorless gum.

[00521] **LCMS:** (ESI) m/z : 253.4 $[M-H]^+$.

[00522] **Step 3: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(5-(1-hydroxyethyl)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (143)**

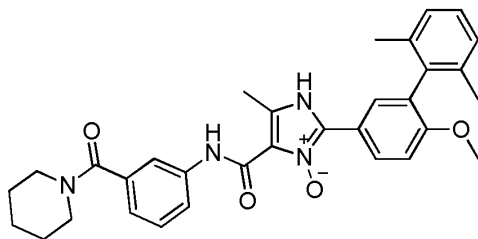


15 [00523] **143** was obtained *via* general procedure from **143-B** and **161-E**

[00524] **LCMS:** (ESI) m/z : 532.2 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 8.32 (s, 1H), 8.01-7.90 (m, 2H), 7.70 (d, J = 7.2 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.35-7.26 (m, 2H), 7.18-7.11 (m, 3H), 4.99 (d, J = 6.4 Hz, 1H), 2.69 (s, 3H), 2.06 (s, 6H), 1.62-1.61 (m 1H), 1.54 (d, J = 6.4 Hz, 3H), 0.74-0.68 (m, 4H).

20 **Synthesis of 139**

[00525] **Step 1: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(piperidine-1-carbonyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (139)**

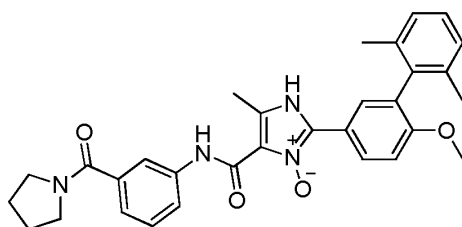


[00526] A mixture of **146-D** (100 mg, 212 μmol , 1.0 *eq*), triethylamine (107 mg, 1.06 mmol, 5.0 *eq*), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (161 mg, 0.423 mmol, 2.0 *eq*) and piperidine (27.0 mg, 318 μmol , 1.5 *eq*) in *N,N*-dimethylformamide (3 mL) was stirred at 20 °C for 12 h. Then the mixture was stirred at 50 °C for 4 h. The mixture was purified by prep-HPLC (neutral condition, column: Waters Xbridge 150 x 25 mm x 5 μm ; mobile phase: [water (10 mM ammonium bicarbonate)- acetonitrile]; B%: 30%-60%, 10 min) to give 20.3 mg (17% yield) of **139** as a white solid.

[00527] **LCMS**: (ESI) m/z : 539.3 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 8.37 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.92-7.89 (m, 2H), 7.65 (td, $J = 1.2, 7.2$ Hz, 1H), 7.45 (t, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 8.8$ Hz, 1H), 7.17-7.13 (m, 2H), 7.10-7.08 (m, 2H), 3.83 (s, 3H), 3.72 (s, 2H), 3.46-3.36 (m, 2H), 2.65 (s, 3H), 2.01 (s, 6H), 1.77-1.64 (m, 4H), 1.57 (s, 2H).

Synthesis of 138

[00528] **Step 1: Synthesis of 2-[3-(2,6-dimethylphenyl)-4-methoxy-phenyl]-5-methyl-3-oxido-*N*-[3-(pyrrolidine-1-carbonyl)phenyl]-1*H*-imidazol-3-ium-4-carboxamide (138)**

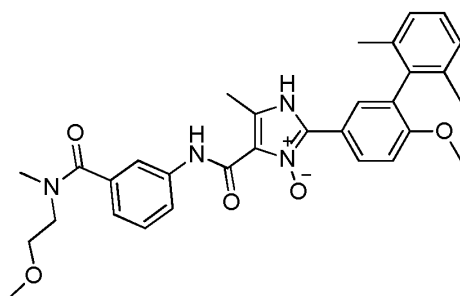


[00529] **138** was obtained *via* similar procedure of **139** from **146-D** and pyrrolidine.

[00530] **LCMS**: (ESI) m/z : 525.3 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 8.37 (dd, $J = 2.4, 8.8$ Hz, 1H), 8.00 (t, $J = 1.6$ Hz, 1H), 7.93 (d, $J = 2.0$ Hz, 1H), 7.68 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.45 (t, $J = 8.0$ Hz, 1H), 7.32-7.26 (m, 2H), 7.17-7.08 (m, 3H), 3.84 (s, 3H), 3.60 (t, $J = 6.8$ Hz, 2H), 3.50 (t, $J = 6.4$ Hz, 2H), 2.65 (s, 3H), 2.03-1.90 (m, 10H).

Synthesis of 141

[00531] **Step 1: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-((2-methoxyethyl)(methyl)carbamoyl)phenyl)carbamoyl)-5-methyl-1*H*-imidazole 3-oxide (141)**

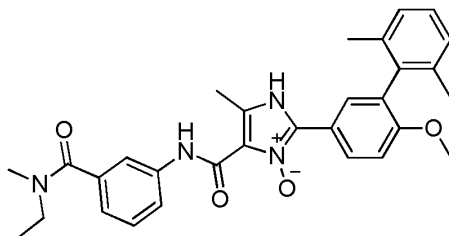


[00532] A mixture of **146-D** (100 mg, 212 μmol , 1.0 *eq*), *N,N*-diisopropylethylamine (54.8 mg, 424 μmol , 2.0 *eq*), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (161 mg, 0.423 mmol, 2.0 *eq*) and 2-methoxy-*N*-methyl-ethanamine (18.9 mg, 212 μmol , 1.0 *eq*) in *N,N*-dimethylformamide (3 mL) was stirred at 20 °C for 16 h. The reaction mixture was filtered and the filtrate was purified by prep-HPLC (formic acid condition. column: Phenomenex Luna C18 150 x 25 mm x 10 μm ; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 41%-71%, 10 min) to give 13.4 mg (10% yield) of **141** as a red solid.

[00533] **LCMS:** (ESI) m/z : 543.3 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 8.36 (dd, $J = 2.0, 8.8$ Hz, 1H), 8.33 (s, 1H), 7.92 (d, $J = 2.4$ Hz, 1H), 7.89 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.47-7.41 (m, 1H), 7.36-7.29 (m, 1H), 7.18-7.13 (m, 2H), 7.10-7.08 (m, 2H), 3.83 (s, 3H), 3.71 (dd, $J = 4.8, 17.6$ Hz, 2H), 3.51-3.41 (m, 3H), 3.28 (s, 2H), 3.11-3.06 (m, 3H), 2.65 (s, 3H), 2.01 (s, 6H).

Synthesis of 140

[00534] **Step 1: Synthesis of 4-((3-(ethyl(methyl)carbamoyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (140)**



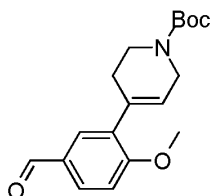
[00535] To a mixture of **146-D** (100 mg, 212 μmol , 1.0 *eq*), *N,N*-diisopropylethylamine (54.8 mg, 424 μmol , 2.0 *eq*), [dimethylamino (triazolo[4,5-*b*]pyridin-3-yloxy) methylidene]-dimethylazanium;hexafluorophosphate (161 mg, 424 μmol , 2.0 *eq*) in *N,N*-dimethylformamide (2 mL) was added *N*-methylethanamine (18.8 mg, 318 μmol , 1.5 *eq*). Then the mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered and the filtrate was purified by prep-HPLC (formic acid condition. column: Phenomenex luna C18 150 x 25 mm x 10 μm ; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 43%-73%, 10 min) to give 10.7 mg (9% yield) of **140** as a pink solid.

[00536] **LCMS:** (ESI) m/z : 513.3 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 8.36 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.91-7.88 (m, 2H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.30 (d, $J = 8.8$ Hz, 1H), 7.16-

7.13 (m, 2H), 7.10-7.08 (m, 2H), 3.83 (s, 3H), 3.61-3.56 (m, 1H), 3.37-3.34 (m, 1H), 3.08-3.00 (m, 3H), 2.64 (s, 3H), 2.01 (s, 6H), 1.27-1.15 (m, 3H).

Synthesis of 162

[00537] **Step 1: Synthesis of *tert*-butyl 4-(5-formyl-2-methoxy-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (162-A)**

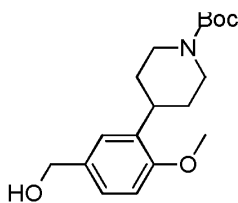


[00538] To a solution of 3-bromo-4-methoxy-benzaldehyde (1.17 g, 5.43 mmol, 1.2 *eq*), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.40 g, 4.53 mmol, 1.0 *eq*), and 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (497 mg, 679 μ mol, 0.15 *eq*) in dioxane (20 mL) and water (2 mL) was added potassium phosphate (1.92 g, 9.06 mmol, 2.0 *eq*). The reaction was degassed and purged with nitrogen and stirred at 80 °C for 12 h. The mixture was quenched by slow addition of saturated sodium sulfite solution (30 mL). Then the suspension was extracted with ethyl acetate (40 mL x 3). The combined organic layer was washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue.

The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 1.30 g (90% yield) of **162-A** as a yellow gum.

[00539] **LCMS:** (ESI) m/z : 317.9.2 [M+H]⁺.

[00540] **Step 2: Synthesis of *tert*-butyl 4-[5-(hydroxymethyl)-2-methoxy-phenyl]piperidine-1-carboxylate (162-B)**

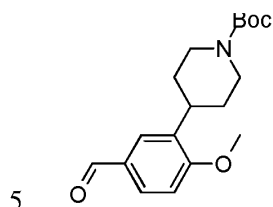


[00541] To a solution **162-A** (500 mg, 1.56 mmol, 1.0 *eq*) in methanol (3 mL) was added palladium on carbon (200 mg, 10% purity). The reaction was degassed and purged with hydrogen, and stirred at 25 °C for 2 h under hydrogen (15 psi). The suspension was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 450 mg (90% yield) of **162-B** as a yellow gum.

[00542] **LCMS:** (ESI) m/z : 304.2 [M-17]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 7.20-7.12 (m, 2H), 6.90

(d, $J = 9.2$ Hz, 1H), 4.51 (s, 2H), 4.19 (d, $J = 13.2$ Hz, 2H), 3.84-3.79 (m, 3H), 3.17-3.09 (m, 1H), 2.86 (s, 2H), 1.77 (d, $J = 12.4$ Hz, 2H), 1.59-1.57 (m, 2H), 1.48 (s, 9H).

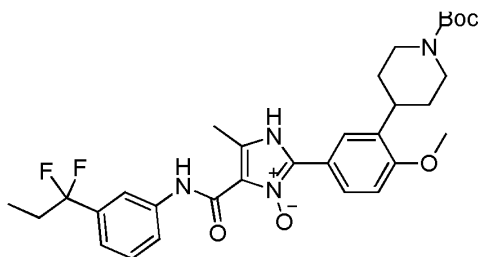
[00543] **Step 3: Synthesis of *tert*-butyl 4-(5-formyl-2-methoxyphenyl)piperidine-1-carboxylate (162-C)**



[00544] To a solution of **162-B** (100 mg, 311 μ mol, 1.0 *eq*) in dichloromethane (2 mL) was added Dess-Martin periodinane (198 mg, 467 μ mol, 1.5 *eq*). The mixture was stirred at 25 °C for 30 min. The reaction was quenched by slow addition of saturated sodium sulfite (15 mL). Then the suspension was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give 90.0 mg (91% yield) of **162-C** as a white solid.

[00545] **LCMS:** (ESI) m/z : 264 $[M-56]^+$.

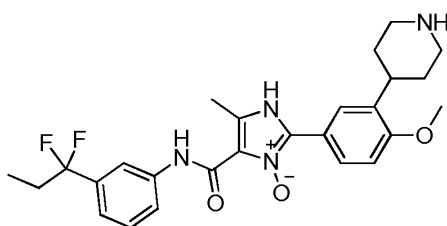
[00546] **Step 4: Synthesis of 2-(3-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-4-methoxyphenyl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (162-D)**



[00547] **162-D** was obtained *via* general procedure from **103-G** and **162-C**.

[00548] **LCMS:** (ESI) m/z : 585.2 $[M+H]^+$.

[00549] **Step 5: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-3-(piperidin-4-yl)phenyl)-5-methyl-1H-imidazole 3-oxide (162)**

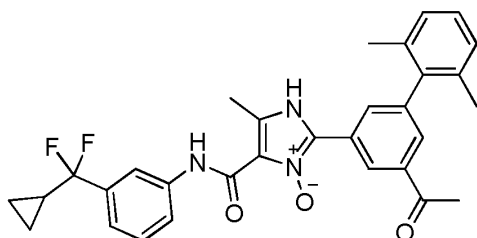


[00550] To a solution of **162-D** (150 mg, 256 μmol , 1.0 *eq*) in ethyl acetate (1.5 mL) was added hydrogen chloride in ethyl acetate (4 M, 1.5 mL). The mixture was stirred at 25 °C for 2 h and concentrated under reduced pressure to give a residue. The crude product was purified by preparative prep-HPLC (column: Phenomenex Synergi C18 150*25mm* 10 μm ; mobile phase: [water(0.1%trifluoroacetic acid)-acetonitrile];B%: 28%-58%,10 min) to give 39.7 mg (26% yield) of **162** as a yellow solid.

[00551] **LCMS**: (ESI) m/z : 485.2 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 8.39 (d, $J = 2.0$ Hz, 1H), 7.96 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.84 (s, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 7.6$ Hz, 1H), 7.20 (d, $J = 8.8$ Hz, 1H), 3.95 (s, 3H), 3.54 (d, $J = 12.4$ Hz, 2H), 3.41-3.33 (m, 1H), 3.19-3.17 (m, 2H), 2.68 (s, 3H), 2.33-2.16 (m, 2H), 2.15 (s, 2H), 2.06-1.96 (m, 2H), 0.99 (t, $J = 7.6$ Hz, 3H).

Synthesis of 142

[00552] **Step 1: Synthesis of 2-(5-acetyl-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (142)**

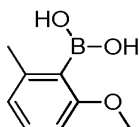


[00553] To a solution of **143** (25.0 mg, 47.0 μmol , 1.0 *eq*) in dichloromethane (3 mL) was added Dess-Martin periodinane (29.9 mg, 70.5 μmol , 1.5 *eq*). The mixture was stirred at 25 °C for 1 h and quenched by slow addition of saturated sodium sulfite (15 mL). Then the suspension was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by preparative prep-HPLC (column: Phenomenex Synergi C18 150*25mm* 10 μm ; mobile phase: [water(0.1%trifluoroacetic acid)- acetonitrile];B%: 63%-93%,10 min) to give 1.80 mg (7% yield) of **142** as a yellow solid.

[00554] **LCMS**: (ESI) m/z : 530.2 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 8.97 (s, 1H), 8.36 (s, 1H), 8.00 (s, 1H), 7.91 (s, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.47-7.43 (m, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.20-7.15 (m, 3H), 2.72 (s, 3H), 2.71 (s, 3H), 2.07 (s, 6H), 1.64 - 1.59 (m, 1H), 0.73-0.68 (m, 4H).

Synthesis of 144

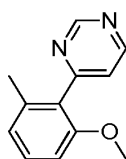
[00555] **Step 1: (2-methoxy-6-methylphenyl)boronic acid (144-A)**



[00556] A solution of 2-bromo-1-methoxy-3-methyl-benzene (2.00 g, 9.95 mmol, 1.0 *eq*) in tetrahydrofuran (40 mL) was cooled to -78 °C and *n*-butyllithium (2.5 M, 4.2 mL, 1.1 *eq*) was added slowly *via* syringe under nitrogen. After stirred for 45 min at -78 °C, trimethyl borate (1.24 g, 12.0 mmol, 1.2 *eq*) was dropwise added to the solution and the mixture was stirred at -78 °C for 15 min and 25 °C for 1 h. The reaction was quenched by adding hydrochloric acid (1 M, 15 mL) and stirred for 1 hr at 25 °C. The suspension was extracted with ethyl acetate (20 mL x 2). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 1.60 g (96% yield) of **144-A** as an off-white solid.

[00557] **LCMS:** (ESI) *m/z*: 167.2 [M+H]⁺.

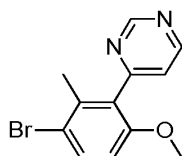
10 [00558] **Step 2: 4-(2-methoxy-6-methylphenyl)pyrimidine (144-B)**



[00559] A mixture of **144-A** (200 mg, 1.20 mmol, 1.1 *eq*), 4-chloropyrimidine (165 mg, 1.10 mmol, 1.0 *eq*, hydrochloride), tetrakis(triphenylphosphine)palladium (127 mg, 110 umol, 0.10 *eq*), sodium carbonate (232 mg, 2.19 mmol, 2.0 *eq*) in water (0.5 mL) and 1,2-dimethoxyethane (2.5 mL) was stirred at 100 °C for 12 hr under nitrogen atmosphere. The mixture was concentrated in vacuum to give the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 140 mg (59% yield) of **144-B** as a yellow solid.

[00560] **LCMS:** (ESI) *m/z*: 201.1 [M+H]⁺.

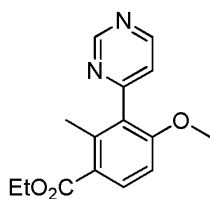
[00561] **Step 3: Synthesis of 4-(3-bromo-6-methoxy-2-methylphenyl)pyrimidine (144-C)**



[00562] To a solution of **144-B** (140 mg, 650 umol, 1.0 *eq*) in acetonitrile (2 mL) was added 1-bromopyrrolidine-2,5-dione (127 mg, 715 umol, 1.1 *eq*). The mixture was stirred at 25 °C for 2 h and then poured into saturated sodium sulfite (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give 180 mg (94% yield) of **144-C** as a yellow solid.

[00563] **LCMS:** (ESI) *m/z*: 279.0 [M+H]⁺.

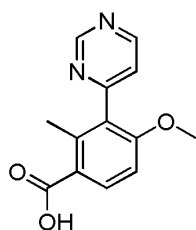
[00564] **Step 4: Synthesis of ethyl 4-methoxy-2-methyl-3-(pyrimidin-4-yl)benzoate (144-D)**



[00565] A mixture of **144-C** (180 mg, 613 μmol , 1.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (672 mg, 918 μmol , 1.5 *eq*) and triethylamine (186 mg, 1.84 mmol, 0.3 mL, 3.0 *eq*) in ethanol (5 mL) was stirred at 70 °C for 36 h under carbonic oxide atmosphere (50 Psi). The mixture was concentrated in vacuum to give the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 120 mg (72% yield) of **144-D** as a yellow liquid.

[00566] **LCMS:** (ESI) m/z : 273.1 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, CDCl_3-d) δ : 9.34 (d, $J = 1.2$ Hz, 1H), 8.80 (d, $J = 5.2$ Hz, 1H), 8.03 (d, $J = 8.8$ Hz, 1H), 7.34-7.30 (m, 1H), 6.87 (d, $J = 8.8$ Hz, 1H), 4.40-4.30 (m, 2H), 3.76 (s, 3H), 2.30 (s, 3H), 1.39 (t, $J = 7.2$ Hz, 3H).

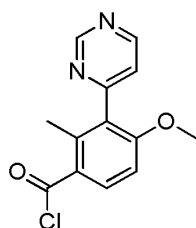
[00567] **Step 5: Synthesis of 4-methoxy-2-methyl-3-(pyrimidin-4-yl)benzoic acid (144-E)**



[00568] To a solution of **144-D** (40.0 mg, 147 μmol , 1.0 *eq*) in ethanol (0.5 mL) was added sodium hydroxide (2 M, 0.5 mL, 6.8 *eq*). The mixture was stirred at 25 °C for 1 h. Then the mixture was diluted with water (10 mL) and extracted with ethyl acetate (8 mL $\times$ 3). The combined organic layer was discarded. The pH of the aqueous layer was adjusted to 5 with 1 M hydrochloric acid and then extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 35 mg (95% yield) of **144-E** as a white solid.

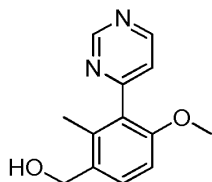
[00569] **LCMS:** (ESI) m/z : 245.0 $[\text{M}+\text{H}]^+$.

[00570] **Step 6: Synthesis of 4-methoxy-2-methyl-3-(pyrimidin-4-yl)benzoyl chloride (144-F)**



[00571] To a solution of **144-E** (35 mg, 139 μmol , 1.0 *eq*) and *N,N*-dimethylformamide (1.02 mg, 13.9 μmol , 1.07 μL , 0.10 *eq*) in dichloromethane (1 mL) was added oxalyl dichloride (26.5 mg, 208 μmol , 18 μL , 1.5 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h and concentrated in vacuum to give 36 mg (crude) of **144-F** as a yellow solid.

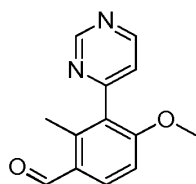
5 [00572] **Step 7: Synthesis of (4-methoxy-2-methyl-3-(pyrimidin-4-yl)phenyl)methanol (144-G)**



[00573] To a solution of **144-F** (36 mg, 137 μmol , 1.0 *eq*) in dichloromethane (0.5 mL) and tetrahydrofuran (0.5 mL) was added sodium tetrahydroborate (51.8 mg, 1.37 mmol, 10 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 h and then diluted with water (10 mL). The pH of the solution was
10 adjusted to 5.0 with 1 M hydrochloric acid and the resulting suspension was extracted with dichloromethane (10 mL $\times$ 3). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 30 mg (crude) of **144-G** as a yellow solid.

[00574] **LCMS:** (ESI) m/z : 230.9 $[\text{M}+\text{H}]^+$.

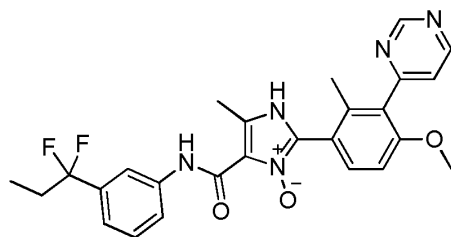
[00575] **Step 8: Synthesis of 4-methoxy-2-methyl-3-(pyrimidin-4-yl)benzaldehyde (144-H)**



15 [00576] To a solution of **144-G** (30.0 mg, 130 μmol , 1.0 *eq*) in dichloroethane (1 mL) was added manganese dioxide (113 mg, 1.30 mmol, 10 *eq*). The mixture was stirred at 20 °C for 12 h. The suspension was filtered and the filtrate was concentrated to give 30 mg (crude) of **144-H** as a yellow solid.

20 [00577] **LCMS:** (ESI) m/z : 229.1 $[\text{M}+\text{H}]^+$.

[00578] **Step 9: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-2-methyl-3-(pyrimidin-4-yl)phenyl)-5-methyl-1*H*-imidazole 3-oxide (144)**

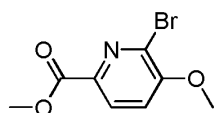


[00579] **144** was obtained *via* general procedure from **103-G** and **144-H**.

[00580] **LCMS**: (ESI) m/z : 494.3 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ : 9.30 (d, J = 1.2 Hz, 1H), 8.88 (d, J = 5.2 Hz, 1H), 7.88 (s, 1H), 7.66-7.60 (m, 2H), 7.54-7.51 (m, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H), 2.55 (s, 3H), 2.26-2.15 (m, 2H), 2.00 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H).

Synthesis of 149

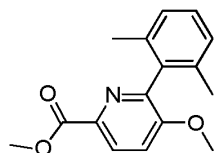
[00581] **Step 1: Synthesis of methyl 6-bromo-5-methoxypicolinate (149-A)**



[00582] To a solution of 6-bromo-5-methoxy-pyridine-2-carboxylic acid (1.00 g, 4.31 mmol, 1.0 *eq*) in methanol (10 mL) was added sulfurous dichloride (2.56 g, 21.6 mmol, 5.0 *eq*). The reaction mixture was stirred at 70 °C for 2 h and then concentrated under reduced pressure to give a residue. The residue was basified to pH>10 by saturated sodium bicarbonate solution (20 mL) and then extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 800 mg (crude) of **149-A** as a white solid.

[00583] **1H NMR** (400 MHz, MeOD- d_4) δ : 8.08 (d, J =8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H).

[00584] **Step 2: Synthesis of methyl 6-(2,6-dimethylphenyl)-5-methoxypicolinate (149-B)**

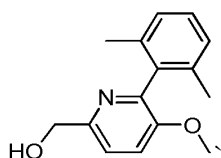


[00585] A mixture of **149-A** (500 mg, 2.03 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (457. mg, 3.05 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (587 mg, 508 μ mol, 0.25 *eq*), potassium phosphate (862 mg, 4.06 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (15 mL) and water (3 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated and aqueous layer was extracted

with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 4/1) to give 300 mg (46% yield) of **149-B** as a yellow solid.

5 [00586] **LCMS:** (ESI) m/z : 272.2 [M+H]⁺.

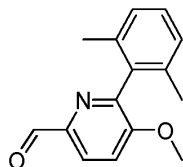
[00587] **Step 3: Synthesis of (6-(2,6-dimethylphenyl)-5-methoxypyridin-2-yl)methanol (149-C)**



[00588] To a solution of **149-B** (100 mg, 317 μ mol, 1.0 *eq*) in tetrahydrofuran (1 mL) was added lithium borohydride (27.6 mg, 1.27 mmol, 4.0 *eq*). The reaction mixture was stirred at 25 °C for 1 h and then
10 heated to 50 °C for 1 h under nitrogen atmosphere. The mixture was quenched by saturated ammonium chloride solution (20 mL) and then extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 75 mg (crude) of **149-C** as a white solid.

[00589] **LCMS:** (ESI) m/z : 244.2 [M+H]⁺.

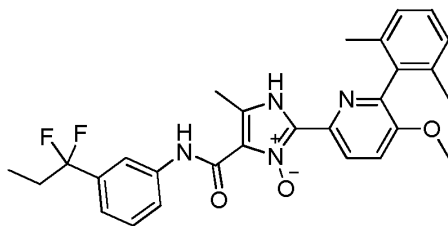
15 [00590] **Step 4: Synthesis of 6-(2,6-dimethylphenyl)-5-methoxypicolinaldehyde (149-D)**



[00591] To a solution of **149-C** (75.0 mg, 308 μ mol, 1.0 *eq*) in dichloroethane (1 mL) was added Dess-Martin periodinane (196 mg, 462 μ mol, 1.5 *eq*). The reaction mixture was stirred at 25 °C for 1 h. and then filtered. The filtrate was concentrated under reduced pressure to give a residue which was purified
20 by silica gel column chromatography (petroleum ether/ethyl acetate= 5/1) to give 60.0 mg (80% yield) of **149-D** as a yellow solid.

[00592] **LCMS:** (ESI) m/z : 242.2 [M+H]⁺.

[00593] **Step 5: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-(2,6-dimethylphenyl)-5-methoxypyridin-2-yl)-5-methyl-1H-imidazole 3-oxide (149)**

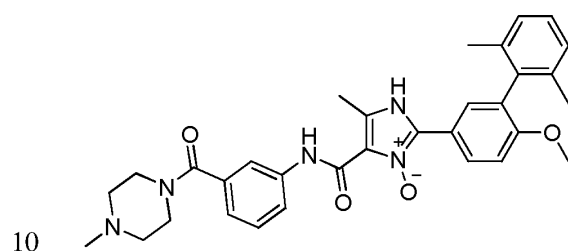


[00594] **149** was obtained *via* general procedure from **149-D** and **103-G**.

[00595] **LCMS**: (ESI) m/z : 507.3 $[M+H]^+$. **¹H NMR** (400 MHz, DMSO- d_6) δ : 13.6 (s, 1H), 13.3 (s, 1H), 9.15 (d, $J=8.8$ Hz, 1H), 7.95 (s, 1H), 7.78 (d, $J=8.8$ Hz, 1H), 7.72 (d, $J=8.4$ Hz, 1H), 7.48 (t, $J=7.6$ Hz, 1H), 7.25-7.19 (m, 2H), 7.15-7.09 (m, 2H), 3.84 (s, 3H), 2.56 (s, 3H), 2.31-2.15 (m, 2H), 1.97 (s, 6H), 0.93 (t, $J=7.2$ Hz, 3H).

Synthesis of 163

[00596] **Step 1: Synthesis of 2-[3-(2,6-dimethylphenyl)-4-methoxy-phenyl]-5-methyl-N-[3-(4-methylpiperazine-1-carbonyl)phenyl]-3-oxido-1H-imidazol-3-ium-4-carboxamide (163)**

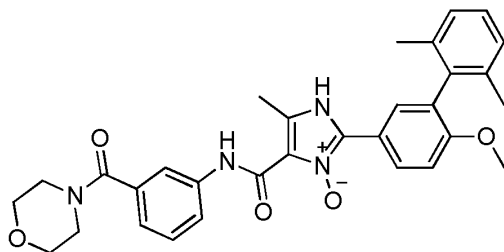


[00597] A mixture of **146-D** (100 mg, 212 μ mol, 1.0 *eq*), *N,N*-diisopropylethylamine (54.8 mg, 424 μ mol, 2.0 *eq*), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (161 mg, 0.423 mmol, 2.0 *eq*) and 1-methylpiperazine (25.4 mg, 254 μ mol, 1.2 *eq*) in *N,N*-dimethylformamide (3 mL) was stirred at 20 °C for 16 h. The reaction mixture was filtered and the filtrate was purified by prep-HPLC (TFA column: Phenomenex Synergi C18 150*25mm*10 μ m; mobile phase: [water(0.1%TFA)-ACN]; B%: 26%-56%, 10min) to give 21.9 mg (18% yield) of **163** as a yellow solid.

[00598] **LCMS**: (ESI) m/z : 554.3 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 8.32 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.95 (d, $J = 2.4$ Hz, 1H), 7.91 (t, $J = 1.6$ Hz, 1H), 7.75-7.72 (m, 1H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.32 (d, $J = 8.8$ Hz, 1H), 7.26 (d, $J = 7.6$ Hz, 1H), 7.18-7.14 (m, 1H), 7.11-7.09 (m, 2H), 3.84 (s, 3H), 3.66-3.37 (m, 4H), 3.26-3.13 (m, 4H), 2.96 (s, 3H), 2.66 (s, 3H), 2.01 (s, 6H).

Synthesis of 148

[00599] **Step 1: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(morpholine-4-carbonyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (148)**

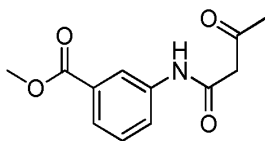


[00600] A mixture of **146-D** (100 mg, 212 μmol , 1.0 *eq*), *N,N*-diisopropylethylamine (54.8 mg, 424 μmol , 2.0 *eq*), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (161 mg, 0.423 mmol, 2.0 *eq*) and morpholine (22.17 mg, 254.50 μmol , 1.2 *eq*) in *N,N*-dimethylformamide (3 mL) was stirred at 20 °C for 16 h. The reaction mixture was filtered and the filtrate was purified by prep-HPLC (FA column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water(0.225%FA)-ACN];B%: 39%-69%,10min) to give 33.0 mg (28% yield) of **148** as a yellow solid.

[00601] **LCMS:** (ESI) m/z : 541.3 $[\text{M}+\text{H}]^+$. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.37 (dd, J = 2.4, 8.8 Hz, 1H), 7.92 (d, J = 2.0 Hz, 2H), 7.69-7.66 (m, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.20-7.08 (m, 4H), 3.84 (s, 3H), 3.77-3.60 (m, 6H), 3.58-3.42 (m, 2H), 2.66 (s, 3H), 2.01 (s, 6H).

Synthesis of 146

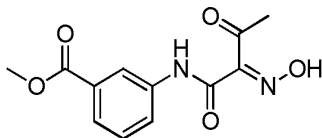
[00602] **Step 1: Synthesis of methyl 3-(3-oxobutanamido)benzoate (146-A)**



[00603] **146-A** was obtained *via* general procedure from methyl 3-aminobenzoate and 4-methyleneoxetan-2-one.

[00604] **LCMS:** (ESI) m/z : 236.1 $[\text{M}+\text{H}]^+$.

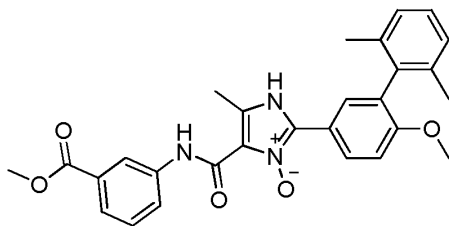
[00605] **Step 2: Synthesis of (E)-methyl 3-(2-(hydroxyimino)-3-oxobutanamido)benzoate (146-B)**



[00606] **146-B** was obtained *via* general procedure from **146-A**.

[00607] **LCMS:** (ESI) m/z : 265.1 $[\text{M}+\text{H}]^+$.

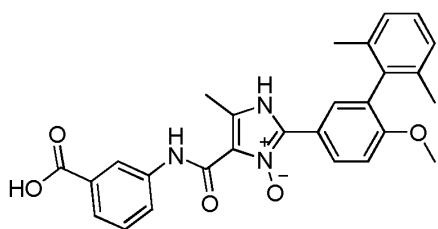
[00608] **Step 3: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(methoxycarbonyl)phenyl)carbamoyl)-5-methyl-1*H*-imidazole 3-oxide (146-C)**



[00609] **146-C** was obtained *via* general procedure from **146-B** and **102-A**.

[00610] **LCMS**: (ESI) m/z : 486.1 $[M+H]^+$.

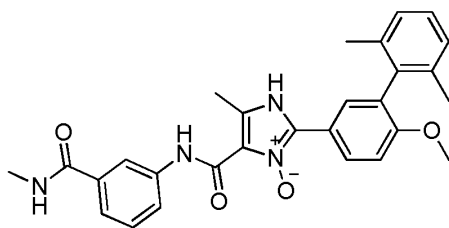
[00611] **Step 4: Synthesis of 4-((3-carboxyphenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (146-D)**



[00612] To a solution of **144-D** (1.00 g, 2.06 mol, 1.0 *eq*) in ethanol (10 mL) was added sodium hydroxide (2 M, 10 mL). The mixture was stirred at 25 °C for 1 h. The pH of the mixture was adjusted to 5 with hydrochloric acid (1 M), and then extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 700 mg (crude) of **146-D** as a white solid.

[00613] **LCMS**: (ESI) m/z : 472.1 $[M+H]^+$.

[00614] **Step 5: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (146)**



[00615] A mixture of **146-D** (300 mg, 636 μ mol, 1.0 *eq*), triethylamine (322 mg, 3.18 mmol, 0.5 mL, 5.0 *eq*), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (484 mg, 1.27 mmol, 2.0 *eq*) and methanamine (64.4 mg, 954 μ mol, 1.5 *eq*, hydrochloride) in *N,N*-dimethylformamide (3 mL) was stirred at 20 °C for 16 h. The mixture was purified by prep-HPLC (neutral condition, column: Waters Xbridge 150 x 25 mm x 5 μ m; mobile phase:

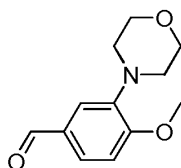
[water (10 mM ammonium bicarbonate)-acetonitrile]; B%: 30%-60%, 10 min) to give 13 mg (4.2% yield) of **146** as a white solid.

[00616] **LCMS:** (ESI) m/z : 485.2 $[M+H]^+$.

[00617] **1H NMR** (400 MHz, MeOD- d_4) δ : 8.37 (dd, J = 2.4, 8.8 Hz, 1H), 8.12 (t, J = 1.6 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.86-7.83 (m, 1H), 7.58-7.56 (m, 1H), 7.47-7.43 (m, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.17-7.13 (m, 1H), 7.10-7.09 (m, 2H), 3.84 (s, 3H), 2.93 (s, 3H), 2.66 (s, 3H), 2.02 (s, 6H).

Synthesis of 150

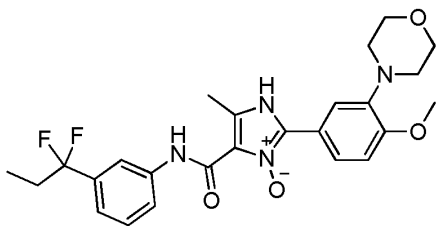
[00618] **Step 1: Synthesis of 4-methoxy-3-morpholinobenzaldehyde (150-A)**



[00619] A suspension of 3-bromo-4-methoxy-benzaldehyde (1.00 g, 4.65 mmol, 1.0 *eq*), morpholine (607 mg, 6.98 mmol, 1.5 *eq*), cesium carbonate (3.03 g, 9.30 mmol, 2.0 *eq*), palladium acetate (104 mg, 465 μ mol, 0.10 *eq*) and dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (433 mg, 930 μ mol, 0.20 *eq*) in toluene (20 mL) was stirred under nitrogen atmosphere at 100 °C for 20 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 200 mg (19% yield) of **150-A** as a yellow solid.

[00620] **1H NMR** (400 MHz, CDCl₃- d) δ : 9.86 (s, 1H), 7.55 (dd, J = 2.0, 8.4 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.91-3.90 (m, 4H), 3.11-3.11 (m, 4H).

[00621] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-3-morpholinophenyl)-5-methyl-1H-imidazole 3-oxide (150)**

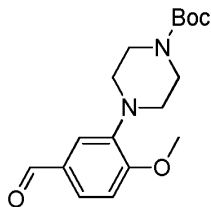


[00622] **150** was obtained *via* general procedure from **150-A** and **103-G**.

[00623] **LCMS:** (ESI) m/z : 487.1 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ : 8.18 (dd, J = 1.6, 8.4 Hz, 1H), 7.98-7.92 (m, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H), 3.80-3.70 (m, 4H), 3.00-3.10 (m, 4H), 2.60 (s, 3H), 2.30-2.20 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).

Synthesis of 164

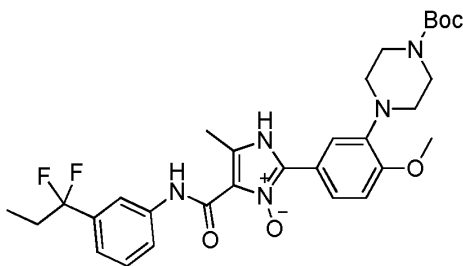
[00624] **Step 1: Synthesis of *tert*-butyl 4-(5-formyl-2-methoxyphenyl)piperazine-1-carboxylate (164-A)**



5 [00625] A suspension of 3-bromo-4-methoxy-benzaldehyde (1.00 g, 4.65 mmol, 1.0 *eq*), *tert*-butyl piperazine-1-carboxylate (1.30 g, 6.98 mmol, 1.5 *eq*), cesium carbonate (3.03 g, 9.30 mmol, 2.0 *eq*), palladium acetate (104 mg, 465 μ mol, 0.10 *eq*) and dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (433 mg, 930 μ mol, 0.20 *eq*) in toluene (20 mL) was stirred under nitrogen atmosphere at 100 °C for 20 h. The reaction mixture was filtered and the filtrate was
10 concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 300 mg (19% yield) of **164-A** as a yellow solid.

[00626] **LCMS:** (ESI) m/z : 321.2 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃-*d*) δ 9.86 (s, 1H), 7.55 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 3.97 (s, 3H), 3.61-3.60 (m, 4H), 3.10-
15 3.00 (m, 4H), 1.49 (s, 9H).

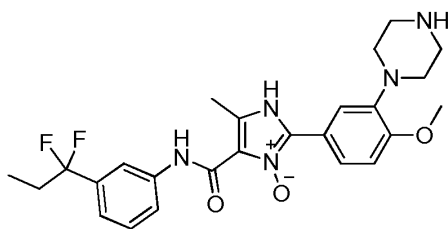
[00627] **Step 2: Synthesis of 2-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-4-methoxyphenyl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (164-B)**



[00628] **164-B** was obtained *via* general procedure from **164-A** and **103-G**.

20 [00629] **LCMS:** (ESI) m/z : 586.2 [M+H]⁺.

[00630] **Step 3: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-3-(piperazin-1-yl)phenyl)-5-methyl-1H-imidazole 3-oxide (164)**

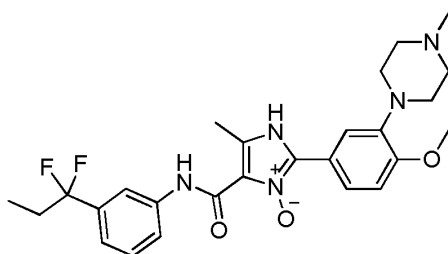


[00631] A solution of **164-B** (120 mg, 204 μ mol, 1.0 *eq*) in hydrogen chloride in ethyl acetate (4 M, 10 mL) was stirred at 25 °C for 30 min. The pH of the mixture was adjusted to 8-9 by saturated aqueous sodium hydroxide (2.0 M). The resulting mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (Phenomenex Gemini C18 column (150 $\times$ 25 mm, 10 μ m); mobile phase: [water (0.1% trifluoroacetic acid)-acetonitrile]; B: 26%-56% acetonitrile, 10 min) to give 14.2 mg (12% yield) of **164** as a white solid.

[00632] **LCMS**: (ESI) m/z : 486.1 $[M+H]^+$. **1H NMR** (400 MHz, $CDCl_3-d$) δ : 10.48 (brs, 1H), 9.33 (s, 2H), 8.02 (d, J = 7.6 Hz, 1H), 7.88 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.8 Hz, 1H), 3.97 (s, 3H), 3.50 (s, 8H), 2.34 (s, 3H), 2.21 (dd, J = 8.0, 15.6 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H).

Synthesis of 165

[00633] **Step 1: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl)-5-methyl-1H-imidazole 3-oxide (165)**



[00634] To a solution of **164** (50.0 mg, 102 μ mol, 1.0 *eq*) in methanol (1 mL) and, acetic acid (0.1 mL) were added formaldehyde (33%, 1 mL) and sodium cyanoborohydride (64.7 mg, 1.03 mmol, 10 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Phenomenex Synergi C18 150*25mm* 10 μ m; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 13%-43%, 10min) to give 11.9 mg (21% yield) of **165** as a white solid.

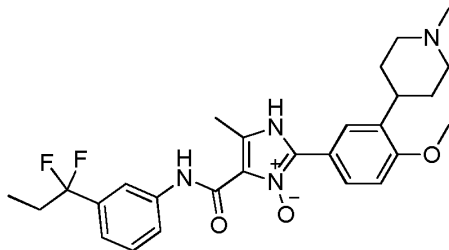
[00635] **LCMS**: (ESI) m/z : 500.2 $[M+H]^+$. **1H NMR** (400 MHz, $CDCl_3-d$) δ 12.9 (brs, 1H), 8.56 (s, 1H), 7.91 (s, 1H), 7.89 (s, 2H), 7.77 (s, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 3.86 (s, 3H), 3.34 (s, 4H), 3.11 (s, 4H), 2.68 (s, 3H), 2.59 (s, 3H), 2.20-2.10 (m, 2H), 1.01

(t, $J = 7.6$ Hz, 3H).

Synthesis of 166

[00636] **Step 1: Synthesis of *N*-[3-(1,1-difluoropropyl)phenyl]-2-[4-methoxy-3-(1-methyl-4-piperidyl)phenyl]-5-methyl-3-oxido-1*H*-imidazol-3-ium-4-carboxamide (166)**

5

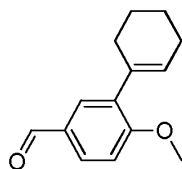


[00637] To a solution of **162** (50.0 mg, 103 μ mol, 1.0 *eq*) in methanol (1 mL) and, acetic acid (0.1 mL) were added formaldehyde (33%, 1 mL) and sodium cyanoborohydride (64.8 mg, 1.03 mmol, 10 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 h and then filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative prep-HPLC (column: Phenomenex Synergi C18 150*25mm* 10 μ m; mobile phase: [water(0.1%trifluoroacetic acid)-acetonitrile]; B%: 28%-58%, 10 min) to give desired compound to give 3.50 mg (7% yield) of **166** as a yellow solid.

[00638] **LCMS:** (ESI) m/z : 499.3 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.44 (d, $J = 2.0$ Hz, 1H), 7.93 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.82 (s, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 7.6$ Hz, 1H), 7.21 (d, $J = 8.8$ Hz, 1H), 3.95 (s, 3H), 3.65 (d, $J = 12.0$ Hz, 2H), 3.35 (t, $J = 3.6$ Hz, 1H), 3.20 (dt, $J = 2.4, 12.4$ Hz, 2H), 2.94 (s, 3H), 2.69 (s, 3H), 2.28-2.18 (m, 2H), 2.17-2.13 (m, 2H), 2.10-2.00 (m, 2H), 0.99 (t, $J = 7.6$ Hz, 3H).

Synthesis of 145

[00639] **Step 1: Synthesis of 6-methoxy-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbaldehyde (145-A)**

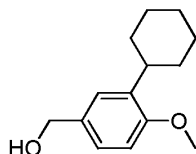


[00640] A mixture of 3-bromo-4-methoxy-benzaldehyde (200 mg, 930 μ mol, 1.0 *eq*), cyclohexen-1-ylboronic acid (117 mg, 930 μ mol, 1.0 *eq*), potassium phosphate (395 mg, 1.86 mmol, 2.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (68.1 mg, 93.0 μ mol, 0.10 *eq*) in dioxane (5 mL) and water (1mL) was stirred at 80 °C for 16 h under nitrogen atmosphere. To the reaction mixture

was added water (20 mL), and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 90.0 mg (44% yield) of **145-A** as a colorless oil.

[00641] LCMS: (ESI) m/z : 217.4 [M+H]⁺.

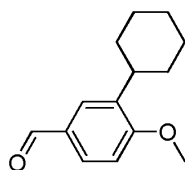
[00642] **Step 2: Synthesis of (3-cyclohexyl-4-methoxyphenyl)methanol (145-B)**



To a solution of **145-A** (90.0 mg, 412 μ mol, 1.0 *eq*) in tetrahydrofuran (3 mL) was added palladium on carbon (30 mg, 10% purity). The reaction was degassed and purged with hydrogen, and stirred at 25 °C for 2 h under hydrogen (15 psi). The suspension was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give 90.0 mg (crude) of **145-B** as a colorless oil.

[00644] LCMS: (ESI) m/z : 203 [M-17]⁺.

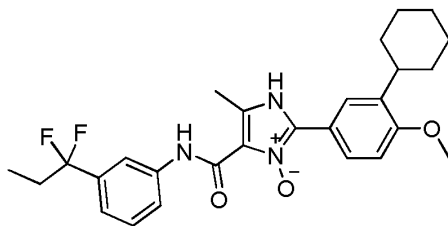
[00645] **Step 3: Synthesis of 3-cyclohexyl-4-methoxybenzaldehyde (145-C)**



To a solution of **145-B** (90.0 mg, 408 μ mol, 1.0 *eq*) in dichloromethane (2 mL) was added Dess-Martin Periodinane (260 mg, 613 μ mol, 1.5 *eq*). The mixture was stirred at 25 °C for 1 h and quenched by slow addition of saturated aqueous sodium sulfite (10 mL). The resulting mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 100 mg (crude) of **145-C** as a colorless oil.

[00647] LCMS: (ESI) m/z : 219.4 [M+H]⁺.

[00648] **Step 4: Synthesis of 2-(3-cyclohexyl-4-methoxyphenyl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (145)**

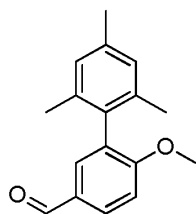


[00649] **145** was obtained *via* general procedure from **145-C** and **103-G**.

[00650] **LCMS**: (ESI) m/z : 484.5 $[M+H]^+$. **¹H NMR** (400 MHz, DMSO- d_6) δ = 13.8 (s, 1H), 13.2 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 3.86 (s, 3H), 2.97-2.92 (m, 1H), 2.61 (s, 3H), 2.29-2.15 (m, 2H), 1.84-1.73 (m, 5H), 1.49-1.34 (m, 4H), 1.31-1.22 (m, 1H), 0.93 (t, J = 7.6 Hz, 3H).

Synthesis of 152

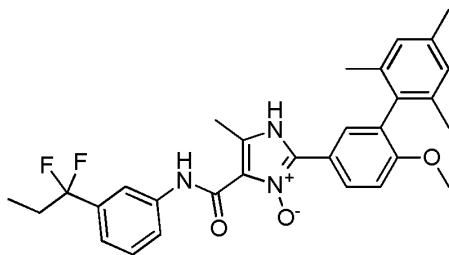
[00651] **Step 1: Synthesis of 6-methoxy-2',4',6'-trimethyl-[1,1'-biphenyl]-3-carbaldehyde (152-A)**



[00652] A mixture of 3-bromo-4-methoxy-benzaldehyde (200 mg, 930 μ mol, 1.0 *eq*), (2,4,6-trimethylphenyl)boronic acid (229 mg, 1.40 mmol, 1.5 *eq*), potassium phosphate (395 mg, 1.86 mmol, 2.0 *eq*), tetrakis[triphenylphosphine]palladium (269 mg, 233 μ mol, 0.25 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 16 h under nitrogen atmosphere. To the reaction mixture was added water (20 mL), and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 100 mg (42% yield) of **152-A** as a yellow solid.

[00653] **LCMS**: (ESI) m/z : 255.4 $[M+H]^+$.

[00654] **Step 2: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (152)**

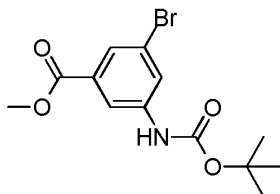


[00655] **152** was obtained *via* general procedure from **152-A** and **103-G**.

[00656] **LCMS**: (ESI) m/z : 520.3 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ : 13.7 (s, 1H), 8.51 (dd, J = 2.0, 8.8 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H), 7.93 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.93 (s, 2H), 3.78 (s, 3H), 2.57 (s, 3H), 2.28 (s, 3H), 2.24-2.12 (m, 2H), 1.92 (s, 6H), 0.92 (t, J = 7.6 Hz, 3H).

Synthesis of 147

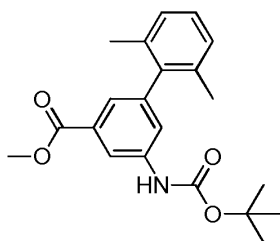
[00657] **Step 1: Synthesis of methyl 3-bromo-5-(tert-butoxycarbonylamino)benzoate (147-A)**



[00658] To a solution of methyl 3-amino-5-bromo-benzoate (2.00 g, 8.69 mmol, 1.0 *eq*) and di-*tert*-butyl dicarbonate (3.79 g, 17.4 mmol, 2.0 *eq*) in tetrahydrofuran (30 mL) was added triethylamine (1.76 g, 17.4 mmol, 2.0 *eq*). The reaction mixture was stirred at 50 °C for 12 h and then concentrated under reduce pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 1.50 g (52% yield) of **147-A** as a white solid.

[00659] **1H NMR** (400 MHz, $CDCl_3$ - d) δ : 7.99 (s, 1H), 7.83-7.81 (m, 2H), 6.63 (s, 1H), 3.92 (s, 3H), 1.53 (s, 9H).

[00660] **Step 2: Synthesis of methyl 5-((tert-butoxycarbonyl)amino)-2',6'-dimethyl-[1,1'-biphenyl]-3-carboxylate (147-B)**

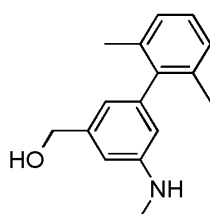


[00661] To a solution of **147-A** (1.50 g, 4.54 mmol, 1.0 *eq*) and (2,6-dimethylphenyl)boronic acid (817 mg, 5.45 mmol, 1.2 *eq*), potassium phosphate (1.93 g, 9.09 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (25

mL) and water (5 mL) was added tetrakis(triphenylphosphine)palladium (787 mg, 681 μmol , 0.15 *eq*). The reaction was degassed and purged with nitrogen and stirred at 100 °C for 12 h under nitrogen atmosphere. To the reaction mixture was added water (30 mL), and the suspension was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/1) to give 1.50 g (93% yield) of **147-B** as a yellow solid.

[00662] ¹H NMR (400 MHz, MeOD-*d*₄) δ : 8.14 (t, *J* = 1.6 Hz, 1H), 7.40 (d, *J* = 1.6 Hz, 2H), 7.13-7.02 (m, 3H), 6.93-6.89 (m, 1H), 3.90 (s, 3H), 2.00 (s, 6H), 1.52 (s, 9H).

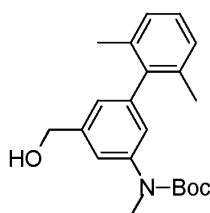
10 [00663] **Step 3: Synthesis of (2',6'-dimethyl-5-(methylanino)-[1,1'-biphenyl]-3-yl)methanol (147-C)**



[00664] To a solution **147-B** (900 mg, 2.53 mmol 1.0 *eq*) in tetrahydrofuran (15 mL) was added aluminum(III) lithium hydride (480 mg, 12.6 mmol, 5.0 *eq*). The mixture was stirred at 75 °C for 12 h and then quenched by saturated ammonium chloride solution (30 mL). The mixture was extracted with ethyl acetate (15 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 450 mg (74% yield) of **147-C** as a yellow gum.

20 [00665] LCMS: (ESI) *m/z*: 242.2 [M+H]⁺.

[00666] **Step 4: Synthesis of *tert*-butyl (5-(hydroxymethyl)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)(methyl)carbamate (147-D)**

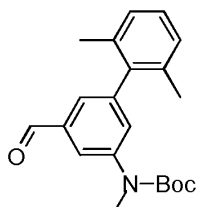


[00667] To a solution of **147-C** (400 mg, 1.66 mmol, 1.0 *eq*) and *tert*-butyl (2-methylpropan-2-yl)oxycarbonyl carbonate (723 mg, 3.32 mmol, 2.0 *eq*) in tetrahydrofuran (3 mL) was added triethylamine (335 mg, 3.32 mmol, 2.0 *eq*). The reaction mixture was stirred at 50 °C for 12 h and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography

(petroleum ether/ethyl acetate, from 10/1 to 1/1) to give 430 mg (76% yield) of **147-D** as a yellow gum.

[00668] ¹H NMR (400 MHz, CDCl₃-d) δ: 7.27 (d, *J* = 1.6 Hz, 1H), 7.19-7.14 (m, 1H), 7.12-7.07 (m, 2H), 6.95 (s, 2H), 4.73 (s, 2H), 3.29 (s, 3H), 2.05 (s, 6H), 1.44 (s, 9H).

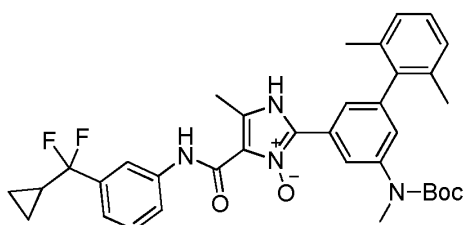
5 [00669] **Step 5: Synthesis of *tert*-butyl (5-formyl-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)(methyl)carbamate (147-E)**



[00670] To a solution of **147-D** (370 mg, 1.08 mmol, 1.0 *eq*) in dichloromethane (2 mL) was added Dess-Martin periodinane (459 mg, 1.08 mmol, 1.0 *eq*). The mixture was stirred at 25 °C for 30 min and then quenched by slow addition of saturated sodium sulfite (15 mL). The suspension was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give 350 mg (95% yield) of **147-E** as a yellow gum.

[00671] LCMS: (ESI) *m/z*: 283.9 [M-51]⁺.

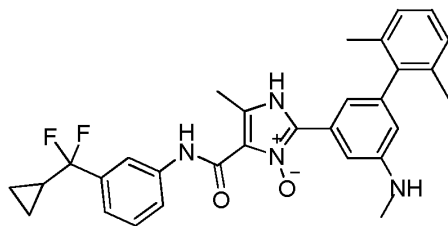
15 [00672] **Step 6: Synthesis of 2-(5-((*tert*-butoxycarbonyl)(methyl)amino)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1*H*-imidazole 3-oxide (147-F)**



[00673] **147-F** was obtained *via* general procedure from **147-E** and **161-E**.

20 [00674] LCMS: (ESI) *m/z*: 617.2 [M+H]⁺.

[00675] **Step 7: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(2',6'-dimethyl-5-(methylamino)-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (147)**



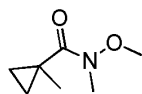
[00676] A solution of **147-F** (70.0 mg, 113 μmol , 1.0 *eq*) in hydrogen chloride in ethyl acetate (4 M, 2 mL) was stirred at 25 °C for 30 min. The mixture was concentrated under reduced pressure to give a residue. The crude product was purified by preparative prep-HPLC (column: Phenomenex Synergi C18
 5 150*25mm* 10 μm ;mobile phase: [water(0.1%trifluoroacetic acid)- acetonitrile];B%: 56%-86%,10 min) to give desired compound to give 13.6 mg (19% yield) of **147** as a yellow solid.

[00677] **LCMS**: (ESI) m/z : 517.3 $[\text{M}+\text{H}]^+$.

[00678] **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 7.97 (s, 1H), 7.90 (t, $J = 1.6$ Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.45 (t, $J = 8.0$ Hz, 1H), 7.34-7.30 (m, 2H), 7.16-7.09 (m, 3H), 6.76 (dd, $J = 1.2, 2.0$ Hz, 1H), 2.96
 10 (s, 3H), 2.67 (s, 3H), 2.09 (s, 6H), 1.66-1.56 (m, 1H), 0.74-0.69 (m, 4H).

Synthesis of 151

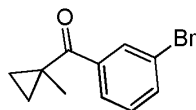
[00679] **Step 1: Synthesis of *N*-methoxy-*N*,1-dimethylcyclopropanecarboxamide (151-A)**



[00680] A solution of 1-methylcyclopropanecarboxylic acid (10.0 g, 99.9 mmol, 1.0 *eq*) and *N,N*-carbonyldiimidazole (19.4 g, 120 mmol, 1.2 *eq*) in dichloromethane (150 mL) was stirred at 25 °C for 1 h. Then to the reaction mixture was added *N*-methoxymethanamine (9.74 g, 99.9 mmol, 1.0 *eq*, hydrochloride) and the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with water (500 mL) and extracted with dichloromethane (100 mL x 3). The combined organic layer was washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under
 20 reduced pressure to give 12.5 g (crude) **151-A** as a yellow oil.

[00681] **^1H NMR** (400 MHz, CDCl_3-d) δ : 3.73 (s, 3H), 3.24 (s, 3H), 1.37 (s, 3H), 1.06-1.00 (m, 2H), 0.58-0.55 (m, 2H).

[00682] **Step 2: Synthesis of (3-bromophenyl)(1-methylcyclopropyl)methanone (151-B)**

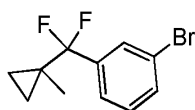


25 [00683] A solution of 1,3-dibromobenzene (24.7 g, 105 mmol, 1.2 *eq*) in tetrahydrofuran (200 mL) was degassed and purged with nitrogen, then chilled to -78 °C. To the solution was dropwise added *n*-

butyllithium (2.5 M, 38 mL, 1.1 *eq*) at -78 °C. After completion of addition, the solution was stirred at -78 °C for 1 h. Then to the reaction was added dropwise a solution of **151-A** (12.5 g, 87.3 mmol, 1.0 *eq*) in tetrahydrofuran (50 mL) at -78 °C. After completion of addition, the reaction mixture was warmed to 25 °C and stirred for 12 h. The reaction was quenched by slow addition of saturated aqueous ammonium chloride (100 mL), and the suspension was extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 9.60 g (46% yield) of **151-B** as a yellow oil.

- 10 [00684] **¹H NMR** (400 MHz, CDCl₃-*d*) δ : 7.20 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.80 (s, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 3.49 (s, 2H), 2.17-2.07 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H).

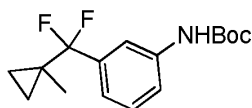
[00685] **Step 3: Synthesis of 1-bromo-3-(difluoro(1-methylcyclopropyl)methyl)benzene (151-C)**



- 15 [00686] A solution of **151-B** (4.80 g, 20.1 mmol, 1.0 *eq*) in diethylaminosulfur trifluoride (64.7 g, 401 mmol, 20 *eq*) was stirred under nitrogen atmosphere at 70 °C for 12 hr. The reaction mixture was quenched with ice water (300 mL) and the resulting suspension was extracted with dichloromethane (100 mL x 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether) to give 3.25 g (62% yield) of **151-C** as a light yellow oil.
- 20

[00687] **¹H NMR** (400 MHz, CDCl₃-*d*) δ : 7.66 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 1.07 (s, 3H), 1.04-1.01 (m, 2H), 0.51-0.48 (m, 2H). **¹⁹F NMR** (376 MHz, CDCl₃-*d*) δ : -101.10.

- 25 [00688] **Step 4: Synthesis of *tert*-butyl (3-(difluoro(1-methylcyclopropyl)methyl)phenyl)carbamate (151-D)**

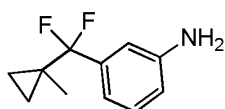


- [00689] A suspension of **151-C** (500 mg, 1.91 mmol, 1.0 *eq*), *tert*-butyl carbamate (448 mg, 3.83 mmol, 2.0 *eq*), palladium acetate (42.9 mg, 191 μ mol, 0.10 *eq*), dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphane (182 mg, 382 μ mol, 0.20 *eq*), cesium carbonate (1.25 g, 3.83 mmol, 2.0 *eq*) in dioxane (10 mL) was stirred at 90 °C for 12 h under nitrogen atmosphere. The mixture was filtered, and the filtrate was diluted with water (20 mL). The resulting suspension was extracted with
- 30

ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 520 mg (91% yield) of **151-D** as a yellow solid.

- 5 [00690] ^1H NMR (400 MHz, CDCl_3 -*d*) δ : 7.51 (d, J = 7.6 Hz, 1H), 7.42 (s, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 6.54 (s, 1H), 1.53 (s, 9H), 1.08 (s, 3H), 1.02-1.00 (m, 2H), 0.46 (d, J = 1.6 Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3 -*d*) δ : -100.83.

[00691] **Step 5: Synthesis of 3-(difluoro(1-methylcyclopropyl)methyl)aniline (151-E)**

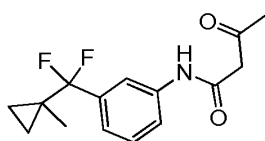


- 10 [00692] A solution of **151-D** (270 mg, 908.05 μmol , 1 *eq*) in hydrogen chloride in ethyl acetate (4 M, 2 mL) was stirred at 25 °C for 30 min. The mixture was concentrated under reduced pressure to give 270mg (crude) of **151-E** as a yellow solid.

[00693] **LCMS:** (ESI) m/z : 198.1 $[\text{M}+\text{H}]^+$.

[00694] **Step 6: Synthesis of N-(3-(difluoro(1-methylcyclopropyl)methyl)phenyl)-3-**

- 15 **oxobutanamide (151-F)**

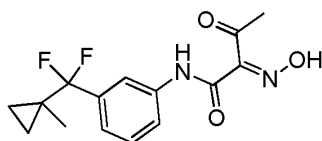


[00695] **151-F** was obtained *via* general procedure from **151-E**.

[00696] **LCMS:** (ESI) m/z : 282.1 $[\text{M}+\text{H}]^+$.

[00697] **Step 7: Synthesis of (E)-N-(3-(difluoro(1-methylcyclopropyl)methyl)phenyl)-2-**

- 20 **(hydroxyimino)-3-oxobutanamide (151-G)**

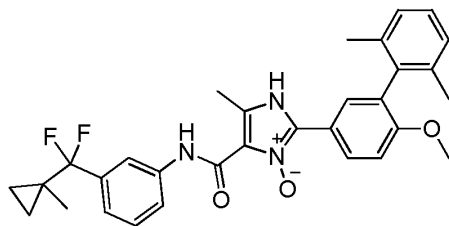


[00698] **151-G** was obtained *via* general procedure from **151-F**.

[00699] **LCMS:** (ESI) m/z : 311.1 $[\text{M}+\text{H}]^+$.

[00700] **Step 8: Synthesis of 4-((3-(difluoro(1-methylcyclopropyl)methyl)phenyl)carbonyl)-2-(6-**

- 25 **methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (151)**

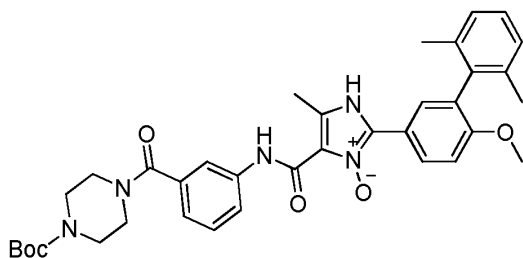


[00701] **151** was obtained *via* general procedure from **151-G**.

[00702] **LCMS:** (ESI) m/z : 532.3 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.38 (dd, J = 8.4, 2.0 Hz, 1H), 7.95 (s, 1H), 7.91 (d, J = 3.0 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.17-7.13 (m, 1H), 7.10-7.09 (m, 2H), 3.84 (s, 3H), 2.66 (s, 3H), 2.02 (s, 6H), 1.08 (s, 3H), 1.03-1.00 (m, 2H), 0.50 (s, 2H).

Synthesis of 153

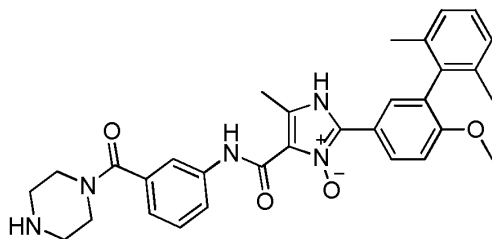
[00703] **Step 1: Synthesis of 4-((3-(4-(tert-butoxycarbonyl)piperazine-1-carbonyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (153-A)**



[00704] A mixture of **146-D** (200 mg, 424 μ mol, 1.0 *eq*), *tert*-butyl piperazine-1-carboxylate;hydrochloride (94.4 mg, 424 μ mol, 1.0 *eq*), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium (241 mg, 636 μ mol, 1.5 *eq*) and *N,N*-diisopropylethylamine (109 mg, 848 μ mol, 2.0 *eq*) in *N,N*-dimethylformamide (5 mL) was stirred at 25°C for 2 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was dissolved in methanol (2 mL) and poured into water (5 mL). The suspension was filtered and the filter-cake was dried in vacuum to give 120 mg (44% yield) of **153-A** as a yellow solid.

[00705] **LCMS:** (ESI) m/z : 640.2 $[M+H]^+$.

[00706] **Step 2: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(piperazine-1-carbonyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (153)**

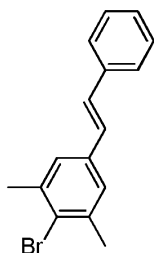


[00707] A solution of **153-A** (150 mg, 234 μmol , 1.0 *eq*) in hydrogen chloride in ethyl acetate (4 M, 3 mL) was stirred at 25 °C for 30 min. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Phenomenex Synergi C18 150*25mm*
 5 10 μm ; mobile phase: [water (0.225% formic acid)-acetonitrile]; B%: 13%-43%, 10min) to give 12 mg (9% yield) of **153** as a white solid.

[00708] **LCMS**: (ESI) *m/z*: 540.2 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{DMSO}-d_6$) δ : 14.3-13.8 (m, 1H), 8.46 (d, *J* = 9.2 Hz, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 7.82 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 9.2 Hz, 1H), 7.2-7.1 (m, 1H), 7.11-7.10 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 3.75 (s, 3H),
 10 3.71-3.70 (m, 4H), 3.01-2.70 (m, 4H), 2.47 (s, 3H), 1.96 (s, 6H).

Synthesis of 154

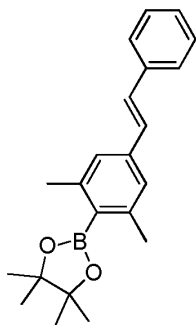
[00709] **Step 1: Synthesis of (*E*)-2-bromo-1,3-dimethyl-5-styrylbenzene (154-A)**



[00710] A mixture of 2,5-dibromo-1,3-dimethyl-benzene (1.64 g, 6.20 mmol, 1.0 *eq*), (*E*)-styrylboronic acid (1.10 g, 7.43 mmol, 1.2 *eq*), cesium carbonate (4.04 g, 12.4 mmol, 2.0 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (453 mg, 620 μmol , 0.10 *eq*) in dioxane (15 mL) and water (1.5 mL) was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and
 20 concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50/1) to give 900 mg (50% yield) of **154-A** as a yellow solid.

[00711] **^1H NMR** (400 MHz, CDCl_3-d) δ : 7.43-7.41 (m, 2H), 7.30-7.26 (m, 2H), 7.21-7.17 (m, 1H), 7.14 (s, 2H), 7.04-6.98 (m, 1H), 6.93-6.88 (m, 1H), 2.36 (s, 6H).

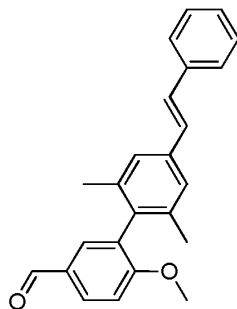
25 [00712] **Step 2: Synthesis of 2-[2,6-dimethyl-4-[(*E*)-styryl]phenyl]-4,4,5,5-tetramethyl-1,3,2-**

dioxaborolane (154-B)

[00713] A mixture of **154-A** (500 mg, 1.74 mmol, 1.0 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.11 g, 4.35 mmol, 2.5 *eq*), 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (127 mg, 174 μ mol, 0.10 *eq*), potassium acetate (513 mg, 5.22 mmol, 3.0 *eq*) in *N,N*-dimethylformamide (7 mL) was stirred at 105 °C for 12 h under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was diluted with water (10 mL). The suspension was extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 530 mg (91% yield) of **154-B** as a yellow oil.

[00714] **LCMS:** (ESI) *m/z*: 335.4 [M+H]⁺.

[00715] **Step 3: Synthesis of (*E*)-6-methoxy-2',6'-dimethyl-4'-styryl-[1,1'-biphenyl]-3-carbaldehyde (154-C)**

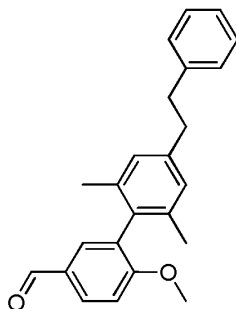


[00716] To a solution of **154-B** (100 mg, 299 μ mol, 1.0 *eq*) in water (0.1 mL) and tetrahydrofuran (2 mL) were added 3-bromo-4-methoxy-benzaldehyde (77.2 mg, 359 μ mol, 1.2 *eq*), potassium hydroxide (100 mg, 1.80 mmol, 6.0 *eq*), tritert-butylphosphonium;tetrafluoroborate (17.4 mg, 59.8 μ mol, 0.20 *eq*) and tri(dibenzylideneacetone)dipalladium(0) (27.4 mg, 30.0 μ mol, 0.10 *eq*). The reaction mixture was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 20 °C for 2 h under nitrogen atmosphere. The reaction mixture was diluted with water (8 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 25.0 mg (24 % yield) of **154-C** as a yellow oil.

[00717] ¹H NMR (400 MHz, CDCl₃-d) δ: 9.94 (s, 1H), 7.94 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 3H), 7.27 (s, 2H), 7.15-7.11 (m, 3H), 3.86 (s, 3H), 2.04 (s, 6H).

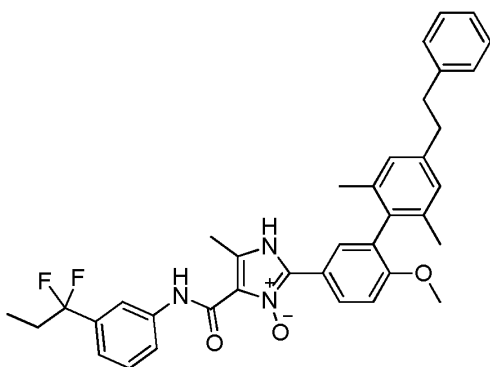
[00718] **Step 4: Synthesis of 6-methoxy-2',6'-dimethyl-4'-phenethyl-[1,1'-biphenyl]-3-carbaldehyde (154-D)**



[00719] A mixture of **154-C** (20.0 mg, 58.4 μmol, 1.0 *eq*), Pd/C (20.0 mg, 10% purity) in ethyl acetate (1 mL), the mixture was degassed and purged with hydrogen for 3 times, and then the mixture was stirred at 20 °C for 1 h under hydrogen (15 Psi) atmosphere. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give 20.0 mg (crude) of **154-D** as a yellow oil.

[00720] ¹H NMR (400 MHz, CDCl₃-d) δ: 9.93 (s, 1H), 7.92 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.36-7.31 (m, 3H), 7.26-7.22 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 2H), 3.86 (s, 3H), 3.00-2.96 (m, 2H), 2.93-2.89 (m, 2H), 2.00 (s, 6H).

[00721] **Step 5: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-4'-phenethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (154)**



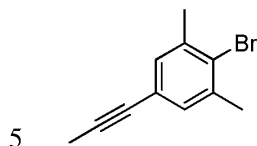
[00722] **154** was obtained *via* general procedure from **154-D** and **103-G**.

[00723] **LCMS:** (ESI) *m/z*: 610.6[M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 13.7 (s, 1H), 13.3-12.9 (m, 1H), 8.54 (d, *J* = 9.2 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.93 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.45

(t, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 4.4$ Hz, 5H), 7.23-7.19 (m, 2H), 7.04 (s, 2H), 3.79 (s, 3H), 2.93-2.89 (m, 2H), 2.87-2.82 (m, 2H), 2.58 (s, 3H), 2.22-2.20 (m, 2H), 1.94 (s, 6H), 0.92 (t, $J = 7.2$ Hz, 3H).

Synthesis of 156

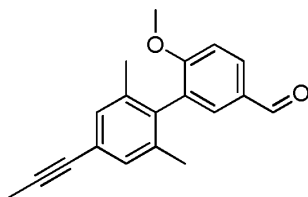
[00724] **Step 1: Synthesis of 2-bromo-1,3-dimethyl-5-prop-1-ynyl-benzene (156-A)**



[00725] A suspension of 2,5-dibromo-1,3-dimethyl-benzene (1.00 g, 3.79 mmol, 1.0 *eq*), prop-1-yne (1 M, 4.6 mL, 1.2 *eq*), Copper iodide (144 mg, 758 μ mol, 0.20 *eq*), triethylamine (3.83 g, 37.9 mmol, 10.0 *eq*) and tetrakis[triphenylphosphine]palladium (438 mg, 379 μ mol, 0.10 *eq*) in tetrahydrofuran (5 mL) was stirred under nitrogen atmosphere at 25 °C for 12 h. The resulting product was filtered to removed the insoluble. The combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0) to give 490 mg (57% yield) of **156-A** as a colorless oil.

[00726] ^1H NMR (400 MHz, CDCl_3 -*d*) δ : 7.11 (s, 2H), 2.37 (s, 6H), 2.03 (s, 3H).

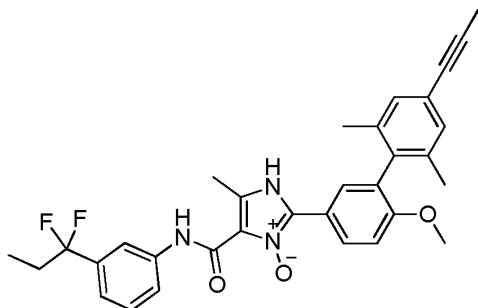
[00727] **Step 2: Synthesis of 6-methoxy-2',6'-dimethyl-4'-(prop-1-yn-1-yl)-[1,1'-biphenyl]-3-carbaldehyde (156-B)**



[00728] To a solution of **156-A** (50.0 mg, 224 μ mol 1.0 *eq*) and (5-formyl-2-methoxy-phenyl)boronic acid (36.3 mg, 202 μ mol, 0.90 *eq*), potassium phosphate (95.1 mg, 448 μ mol, 2.0 *eq*) in 1,2-dimethoxyethane (2 mL) and water (0.4 mL) was added tetrakis[triphenylphosphine]palladium (64.7 mg, 56.0 μ mol, 0.25 *eq*). The reaction was degassed and purged with nitrogen and then stirred at 100 °C for 12 h under nitrogen atmosphere. To the reaction mixture was added water (5 mL). The resulting suspension was extracted with ethyl acetate (5 mL x 3). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 7/1) to give 30.0 mg (48% yield) of **156-B** as a colorless oil.

[00729] LCMS: (ESI) m/z : 279.2 $[\text{M}+\text{H}]^+$.

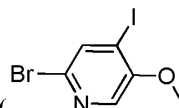
[00730] **Step 3: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-4'-(prop-1-yn-1-yl)-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (156)**



[00731] **156** was obtained *via* general procedure from **103-G** and **156-B**.

[00732] **LCMS**: (ESI) m/z : 544.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.38 (dd, J = 1.6, 8.4 Hz, 1H), 7.94-7.89 (m, 2H), 7.72-7.67 (m, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.11 (s, 2H), 3.84 (s, 3H), 2.66 (s, 3H), 2.26-2.19 (m, 1H), 2.18 (s, 1H), 2.03 (s, 3H), 1.98 (s, 6H), 0.98 (t, J = 7.6 Hz, 3H).

Synthesis of

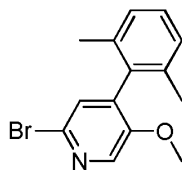


Step 1: Synthesis of 2-bromo-4-iodo-5-methoxypyridine (

[00733] A solution of 2-bromo-5-fluoro-4-iodo-pyridine (1.80 g, 5.96 mmol, 1.0 *eq*) in sodium methoxide (10 mL) was stirred at 60 °C for 2 h under nitrogen atmosphere. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 1.20 g (crude) of as a yellow solid.

[00734] **LCMS**: (ESI) m/z : 313.9 $[M+H]^+$.

[00735] **Step 2: Synthesis of 2-bromo-4-(2,6-dimethylphenyl)-5-methoxypyridine (**

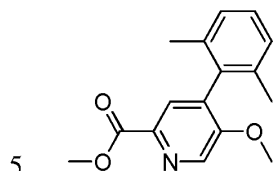


[00736] To a solution of **157-A** (1.00 g, 3.19 mmol, 1.0 *eq*) and (2,6-dimethylphenyl)boronic acid (238 mg, 1.59 mmol, 0.5 *eq*), potassium phosphate (1.35 g, 6.37 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (25 mL) and water (5 mL) was added tetrakis(triphenylphosphine)palladium (920 mg, 796 μ mol, 0.25 *eq*). The reaction was degassed and purged with nitrogen and then stirred at 100 °C for 12 h under nitrogen atmosphere. To the reaction mixture was added water (30 mL), and the suspension was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue

was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 50.0 mg (5% yield) of as a yellow solid.

[00737] **LCMS:** (ESI) m/z : 294.1 [M+H]⁺.

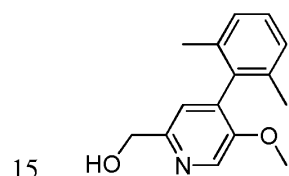
[00738] **Step 3: Synthesis of methyl 4-(2,6-dimethylphenyl)-5-methoxypicolinate (**



[00739] To a solution of (50.0 mg, 171 μ mol, 1.0 *eq*) in methanol (1 mL) were added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (25.0 mg, 34.2 μ mol, 0.20 *eq*) and triethylamine (52.0 mg, 513 μ mol, 3.0 *eq*). The reaction mixture was degassed under vacuum and purged with carbonic oxide for 3 times, and then the mixture was stirred at 80 °C for 12 h under carbonic oxide (50 Psi) atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 40.0 mg (75% yield) of as a white solid.

[00740] **LCMS:** (ESI) m/z : 272.4[M+H]⁺.

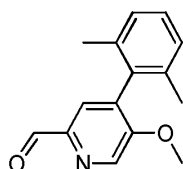
[00741] **Step 4: Synthesis of (4-(2,6-dimethylphenyl)-5-methoxypyridin-2-yl)methanol (**



[00742] To a solution of **C** (40 mg, 128 μ mol, 1.0 *eq*) in tetrahydrofuran (1 mL) was added lithium borohydride (11.0 mg, 500 μ mol, 4.0 *eq*). The reaction mixture was stirred at 25 °C for 1 h and then heated to 50 °C for 1 h under nitrogen atmosphere. The mixture was quenched with saturated ammonium chloride solution (50 mL) and then extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 30 mg (crude) of as a white solid.

[00743] **LCMS:** (ESI) m/z : 244.2[M+H]⁺.

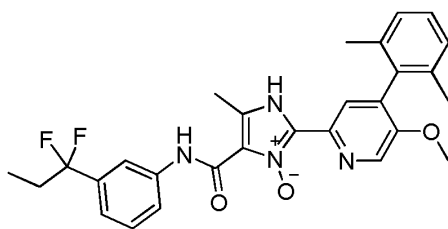
[00744] **Step 5: Synthesis of 4-(2,6-dimethylphenyl)-5-methoxypicolinaldehyde (**



[00745] To a solution of **157-D** (75.0 mg, 308 μmol , 1.0 *eq*) in dichloroethane (1 mL) was added Dess-Martin periodinane (196 mg, 462 μmol , 1.5 *eq*). The reaction mixture was stirred at 25 °C for 1 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate= 5/1) to give
 5 60.0 mg (80% yield) of **E** as a yellow solid

[00746] **LCMS**: (ESI) m/z : 242.0[M+H]⁺.

[00747] **Step 6: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(4-(2,6-dimethylphenyl)-5-methoxypyridin-2-yl)-5-methyl-1H-imidazole 3-oxide (**

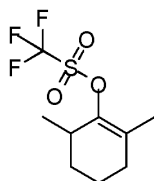


10 [00748] was obtained *via* general procedure from **E** and **103-G**.

[00749] **LCMS**: (ESI) m/z : 507.1[M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 8.68 (s, 1H), 8.61 (s, 1H), 7.93 (s, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.26-7.19 (m, 2H), 7.17-7.10 (m, 2H), 3.96 (s, 3H), 2.70 (s, 3H), 2.24-2.12 (m, 2H), 2.04 (s, 6H), 0.97 (t, *J* = 7.6 Hz, 3H).

Synthesis of 155

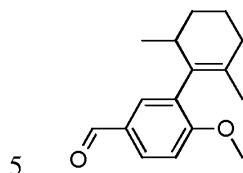
15 [00750] **Step 1: Synthesis of 2,6-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (155-A)**



[00751] To a solution of 2,6-dimethylcyclohexanone (2.00 g, 15.9 mmol, 1.0 *eq*) in tetrahydrofuran (25 mL) was added dropwise lithium bis(trimethylsilyl)amide (1.0 M, 14 mL, 0.90 *eq*) at -78 °C. After addition, the mixture was stirred at -78 °C for 45 min. Then a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (0.56 M, 25 mL, 0.90 *eq*) in tetrahydrofuran (10 mL) was
 20 added dropwise at -78 °C. The mixture was allowed to warm to 20 °C and stirred for 12 h. The mixture was quenched by slow addition of saturated aqueous ammonium chloride (60 mL). The resulting suspension was extracted with ethyl acetate (60 mL x 3). The combined organic layer was washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure
 25 to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 30/1) to give 2.50 g (61% yield) of **155-A** as a yellow oil.

[00752] ¹H NMR (400 MHz, CDCl₃-d) δ: 2.60-2.55 (m, 1H), 2.20-2.06 (m, 2H), 1.97-1.89 (m, 1H), 1.76 (s, 3H), 1.72-1.62(m, 1H), 1.61-1.52 (m, 1H), 1.48-1.30 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H).

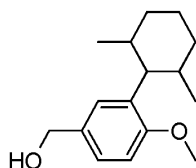
[00753] **Step 2: Synthesis of 6-methoxy-2',6'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbaldehyde (155-B)**



[00754] A mixture of (5-formyl-2-methoxy-phenyl)boronic acid (200 mg, 1.11 mmol, 1.0 *eq*), **155-A** (344 mg, 1.33 mmol, 1.2 *eq*), tetrakis[triphenylphosphine]palladium (321 mg, 278 umol, 0.25 *eq*), potassium phosphate (472 mg, 2.22 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (0.5 mL) was stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50/1) to give 250 mg (92% yield) of **155-B** as a colorless oil.

[00755] LCMS: (ESI) *m/z*: 245.4 [M+H]⁺.

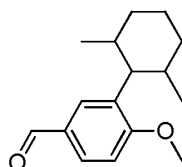
[00756] **Step 3: Synthesis of (3-(2,6-dimethylcyclohexyl)-4-methoxyphenyl)methanol (155-C)**



15 [00757] To a solution of **155-B** (100 mg, 409 umol, 1.0 *eq*) in methanol (3 mL) was added palladium on carbon (100 mg, 10% purity). The suspension was stirred under hydrogen atmosphere (50 psi) at 70 °C for 16 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50/1) to give 20.0 mg (20% yield) of **155-C** as a yellow oil.

20 [00758] ¹H NMR (400 MHz, CDCl₃-d) δ: 7.15-7.13 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.62 (s, 2H), 3.80 (s, 3H), 2.50 (t, *J* = 10.8 Hz, 1H), 1.81-1.75 (m, 2H), 1.58-1.40 (m, 4H), 1.17-1.07 (m, 2H), 0.61 (d, *J* = 6.4 Hz, 6H).

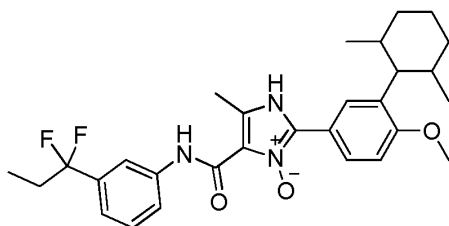
[00759] **Step 4: Synthesis of 3-(2,6-dimethylcyclohexyl)-4-methoxybenzaldehyde (155-D)**



[00760] To a solution of **155-C** (20.0 mg, 80.5 μmol , 1.0 *eq*) in dichloromethane (1 mL) was added Dess-Martin Periodinane (51.2 mg, 121 μmol , 1.5 *eq*). The mixture was stirred at 25 °C for 1 h. and then quenched by slow addition of saturated aqueous sodium sulfite (10 mL). The resulting mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 40.0 mg (crude) of **155-D** as a yellow solid.

[00761] **LCMS:** (ESI) m/z : 247.4 $[\text{M}+\text{H}]^+$.

[00762] **Step 5: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(3-(2,6-dimethylcyclohexyl)-4-methoxyphenyl)-5-methyl-1H-imidazole 3-oxide (155)**



10

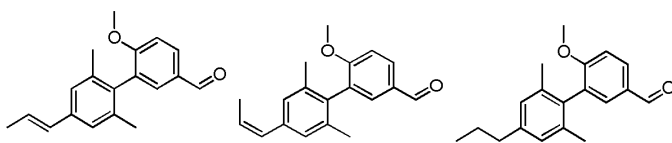
[00763] **155** was obtained *via* general procedure from **155-D** and **103-G**.

[00764] **LCMS:** (ESI) m/z : 512.4 $[\text{M}+\text{H}]^+$. **¹H NMR** (400 MHz, DMSO-*d*₆) δ : 8.26-8.23 (m, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.91 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 2.57 (s, 3H), 2.46-2.43 (m, 1H), 2.23-2.13 (m, 2H), 1.77-1.70 (m, 2H), 1.58-1.38 (m, 4H), 1.09-1.00 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H), 0.53 (d, J = 6.4 Hz, 6H).

15

Synthesis of 158 & 159 & 160

[00765] **Step 1: Synthesis of 3-[2,6-dimethyl-4-[(*E*)-prop-1-enyl]phenyl]-4-methoxy-benzaldehyde (159-A), 3-[2,6-dimethyl-4-[(*Z*)-prop-1-enyl]phenyl]-4-methoxy-benzaldehyde (160-A) & 6-methoxy-2',6'-dimethyl-4'-propyl-[1,1'-biphenyl]-3-carbaldehyde (158-A)**



20

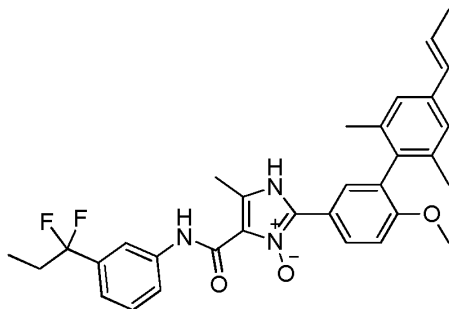
159-A**160-A****158-A**

[00766] To a solution of **156-B** (30.0 mg, 1.0 *eq*) in ethanol (2 mL) were added lindlar catalyst (10.0 mg, 10% purity). The suspension was stirred under hydrogen atmosphere (15 psi.) at 25 °C for 2 h. The mixture was filtered and rinsed with 5 mL of ethanol. The filtrate was concentrated under reduced pressure to give 23.0 mg (crude) mixture of **159-A**, **160-A**, **158-A** as a colorless oil.

25

[00767] **LCMS:** (ESI) m/z : 281.2, 283.2 $[\text{M}+\text{H}]^+$.

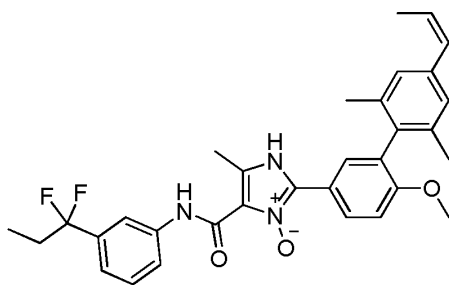
[00768] **Step 2: Synthesis of (E)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-4'-(prop-1-en-1-yl)-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (159)**



[00769] **159** was obtained *via* general procedure from **103-G** and **159-A**.

5 [00770] **LCMS:** (ESI) m/z : 546.3 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.37 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.93-7.88 (m, 2H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.29 (d, $J = 8.8$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.08 (s, 2H), 6.42-6.34 (m, 1H), 6.33-6.22 (m, 1H), 3.83 (s, 3H), 2.65 (s, 3H), 2.21-2.15 (m, 2H), 1.99 (s, 6H), 1.89 (d, $J = 1.2$ Hz, 3H), 0.98 (t, $J = 7.6$ Hz, 3H).

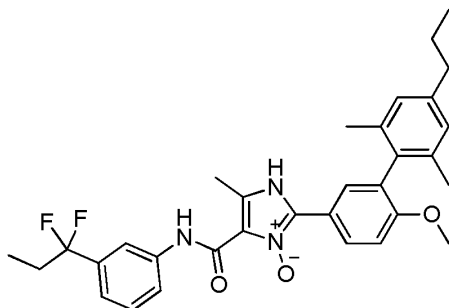
[00771] **(Z)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-4'-(prop-1-en-1-yl)-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (160)**



[00772] **160** was obtained *via* general procedure from **103-G** and **160-A**.

15 [00773] **LCMS:** (ESI) m/z : 546.3 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.37 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.95-7.89 (m, 2H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.29 (d, $J = 8.8$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.04 (s, 2H), 6.40 (dd, $J = 2.0, 12.0$ Hz, 1H), 5.77 (qd, $J = 6.8, 11.6$ Hz, 1H), 3.84 (s, 3H), 2.64 (s, 3H), 2.22-2.15 (m, 2H), 2.02 (s, 6H), 1.93 (dd, $J = 1.6, 7.2$ Hz, 3H), 0.98 (t, $J = 7.2$ Hz, 3H).

[00774] **4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-4'-propyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (158)**

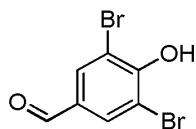


[00775] **158** was obtained *via* general procedure from **103-G** and **158-A**.

[00776] **LCMS:** (ESI) m/z : 548.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.39-8.34 (m, 1H), 7.91 (d, $J = 8.4$ Hz, 2H), 7.71-7.67 (m, 1H), 7.44 (t, $J = 8.4$ Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 6.92 (s, 2H), 3.83 (s, 3H), 2.65 (s, 3H), 2.58-2.53 (m, 2H), 2.21-2.14 (m, 2H), 1.99 (s, 6H), 1.68-1.64 (m, 2H), 1.00-0.96 (m, 6H).

Synthesis of 169

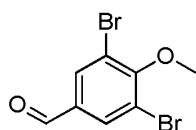
[00777] **Step 1: Synthesis of 3,5-dibromo-4-hydroxy-benzaldehyde (169-A)**



[00778] To a solution of 4-hydroxybenzaldehyde (10.0 g, 81.89 mmol, 1 eq) in MeOH (100 mL) was added bromine (26.2 g, 164 mmol, 2.0 eq) dropwise at 0°C. Then the solution was stirred at 15°C for 1 hr. The resulting solution was concentrated under reduced pressure to give 22.9 g (100% yield) of **169-A** as a light yellow solid.

[00779] **LCMS:** (ESI) m/z : 279.0 $[M-H]^-$. **1H NMR** (400 MHz, DMSO- d_6) δ : 9.78 (s, 1H), 8.04 (s, 2H), 3.42 (q, $J = 7.2$ Hz, 1H), 1.04 (t, $J = 7.2$ Hz, 2H).

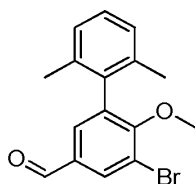
[00780] **Step 2: Synthesis of 3,5-dibromo-4-methoxy-benzaldehyde (169-B)**



[00781] A mixture of **169-A** (4.00 g, 14.3 mmol, 1.0 eq), methyl iodide (2.03 g, 14.3 mmol, 1.0 eq) and potassium carbonate (1.97 g, 14.3 mmol, 1.0 eq) in dimethyl formamide (30 mL) was stirred at 20°C for 16 hr. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (40 mL x 3). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, concentrated. The crude was purified by reversed phase column (FA) to afford 3.10 g (74% yield) of **169-B** as a white solid.

[00782] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.90 (s, 1H), 8.18 (s, 2H), 3.89 (s, 3H).

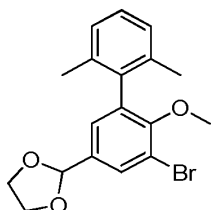
[00783] **Step 3: Synthesis of 3-bromo-5-(2,6-dimethylphenyl)-4-methoxy-benzaldehyde (169-C)**



[00784] A suspension of **169-B** (2.50 g, 8.51 mmol, 1.0 eq), (2,6-dimethylphenyl)boronic acid (1.53 g, 10.2 mmol, 1.2 eq), tetrakis(triphenylphosphine) palladium (295 mg, 255 μmol, 0.03 eq), potassium phosphate (2.35 g, 11.1 mmol, 1.3 eq) in dioxane (80 mL) and water (20 mL) was stirred at 100°C under nitrogen atmosphere for 16 hr. The suspension was concentrated and the residue was dilute with brine (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layer was concentrated to afford the crude product which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20/1) to afford 2.60 g (crude) **169-C** as a white solid.

[00785] **LCMS:** (ESI) *m/z*: 319.0 [M+H]⁺.

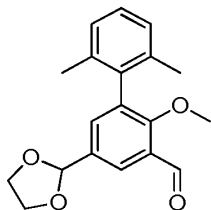
[00786] **Step 4: Synthesis of 2-[3-bromo-5-(2,6-dimethylphenyl)-4-methoxy-phenyl]-1,3-dioxolane (169-D)**



[00787] A mixture of **169-C** (2.60 g, 440 μmol, 1.0 eq), ethylene glycol (2.73 g, 4.40 mmol, 10.0 eq), p-toluenesulfonic acid monohydrate (418 mg, 2.20 mmol, 0.5 eq) and 4A molecular sieve (1.00 g) in toluene (30 mL) was stirred at 110°C for 14 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column (petroleum ether/ethyl acetate=10/1) and then by reversed phase column (60%~ 80% of acetonitrile in water, 0.05% of formic acid) to afford 1.5 g (94% yield) of **169-D** as a colorless gum.

[00788] **LCMS:** (ESI) *m/z*: 363.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃-*d*) δ: 7.71 (d, *J* = 2.0 Hz, 1H), 7.25 - 7.09 (m, 4H), 5.77 (s, 1H), 4.17 - 4.08 (m, 2H), 4.08 - 4.00 (m, 2H), 3.43 (s, 3H), 2.07 (s, 6H).

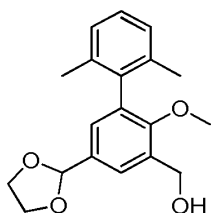
[00789] **Step 5: Synthesis of 3-(2,6-dimethylphenyl)-5-(1,3-dioxolan-2-yl)-2-methoxy-benzaldehyde (169-E)**



[00790] To a solution of **169-D** (1.50 g, 4.12 mmol, 1.0 eq) in tetrahydrofuran (10 mL) was added n-butyl lithium (2.5 M, 2.47 mL, 1.5 eq) dropwise at -70°C under nitrogen atmosphere. After 10 min, dimethyl formamide (602 mg, 8.23 mmol, 2.0 eq) was added and the reaction was stirred at this
 5 temperature for 1 hr. The reaction was quenched by addition of saturated ammonium chloride (20 mL) at 0°C. The suspension was extracted with ethyl acetate (10 mL x 2), dried over anhydrous sodium sulfate, concentrated to give 1.29 g (crude) of **169-E** as a yellow oil.

[00791] **LCMS:** (ESI) m/z : 313.1 $[M+H]^+$.

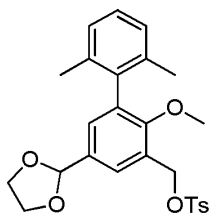
[00792] **Step 6: Synthesis of (5-(1,3-dioxolan-2-yl)-2-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methanol (169-F)**
 10



[00793] To a solution of **169-E** (1.00 g, 3.20 mmol, 1.0 eq) in tetrahydrofuran (20 mL) was added lithium aluminum hydride (122 mg, 3.20 mmol, 1.0 eq) at portions. The reaction was stirred at 15°C for 1 hr. The reaction was quenched by saturated sodium potassium tartrate (50 mL) and extracted with ethyl
 15 acetate (30 mL x 2). The combined organic layer was concentrated under reduced pressure to afford the crude. The crude was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1) to afford 0.34 g (30% yield) of **169-F** as colorless gum.

[00794] **LCMS:** (ESI) m/z : 315.2 $[M+H]^+$. **¹H NMR** (400 MHz, CDCl₃-*d*) δ : 7.51 (d, J = 2.0 Hz, 1H), 7.23 - 7.11 (m, 4H), 5.81 (s, 1H), 4.79 (s, 2H), 4.19 - 4.11(m, 3H), 4.10 - 4.03 (m, 2H), 3.38 (s, 3H),
 20 2.10 (s, 6H).

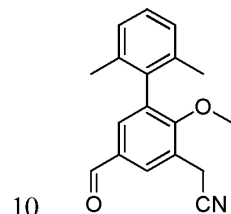
[00795] **Step 7: Synthesis of (5-(1,3-dioxolan-2-yl)-2-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methyl 4-methylbenzenesulfonate (169-G)**



[00796] To a solution of **169-F** (0.30 g, 840 μmol , 1.0 eq) in tetrahydrofuran (10 mL) was added sodium hydride (33.6 mg, 840 μmol , 60% purity, 1.0 eq). After 5 min, paratoluensulfonyl chloride (160 mg, 840 μmol , 1.0 eq) was added and the mixture was stirred at 10°C for 12 hr to give a white suspension. The suspension was diluted with ethyl acetate (10 mL) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with 20% of ethyl acetate in petroleum ether to afford 80 mg (crude) of **169-G** as a colorless gum.

[00797] **LCMS:** (ESI) m/z : 469.2 $[\text{M}+\text{H}]^+$.

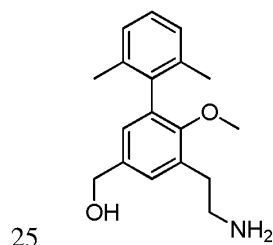
[00798] **Step 8: Synthesis of 2-(5-formyl-2-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)acetonitrile (169-H)**



[00799] To a solution of **169-G** (80 mg, crude) in dimethyl sulfoxide (2 mL) was added sodium cyanide (20 mg, 408 μmol). The mixture was stirred at 10°C for 14 hr. Then another batch of sodium cyanide (40 mg, 816 μmol) was added and the reaction was stirred for another 2 hr. Then the solution was diluted with ethyl acetate (30 mL) and treated with sodium hypochlorite (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layer was washed with brine (10 mL), dried over sodium sulfate, concentrated to afford the crude product which was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water(0.225%FA)-ACN]; B%: 48%-78%, 10 min) and lyophilized to afford 20 mg of **169-H** as a colorless gum.

20 [00800] **LCMS:** (ESI) m/z : 280.2 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, CDCl_3-d) δ : 9.96 (s, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.26 - 7.20 (m, 1H), 7.19 - 7.10 (m, 2H), 3.81 (s, 2H), 3.42 (s, 3H), 2.08 (s, 6H).

[00801] **Step 9: Synthesis of (5-(2-aminoethyl)-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol (169-I)**

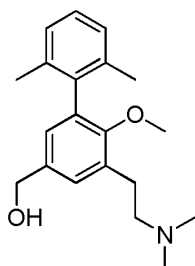


[00802] To a solution of **169-H** (20 mg, 70.7 μmol , 1.0 eq) in isopropanol (6 mL) and hydrochloride

acid (1 M, 100 μ L, 1.42 eq) was added palladium on carbon (10 mg, 10% purity). Then the mixture was stirred at hydrogen atmosphere for 48 hr at 10°C. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 22.7 mg of **169-I** (HCl salt) as a white solid.

[00803] LCMS: (ESI) m/z : 286.2 $[M+H]^+$.

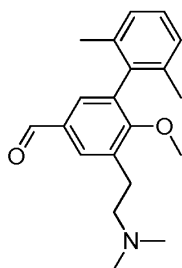
5 [00804] **Step 10: Synthesis of (5-(2-(dimethylamino)ethyl)-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol (169-J)**



[00805] A mixture of **169-I** hydrochloride (22.7 mg, 70.7 μ mol), paraformaldehyde (80 mg) and palladium on carbon (10 mg, 10% purity) in methanol (6 mL) was stirred at 10°C under hydrogen atmosphere (15 psi) for 2 hr. The mixture was filtered and the filtrate was concentrated. The residue was purified by prep-TLC (tetrahydrofuran/methanol/ammonia water = 80/5/2) to afford 18 mg of **169-J** as a colorless oil.

[00806] LCMS: (ESI) m/z : 314.2 $[M+H]^+$. ^1H NMR (400 MHz, CDCl_3 - d) δ : 7.23 (s, 1H), 7.21 - 7.15 (m, 1H), 7.14 - 7.07 (m, 2H), 6.99 (s, 1H), 5.01 (d, J = 1.2 Hz, 1H), 4.66 (s, 2H), 3.32 (d, J = 1.2 Hz, 3H), 2.99 - 2.84 (m, 2H), 2.74 - 2.58 (m, 2H), 2.40 (br s, 6H), 2.28 (s, 3H), 2.08 (s, 6H).

15 [00807] **Step 11: Synthesis of 5-(2-(dimethylamino)ethyl)-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (169-K)**

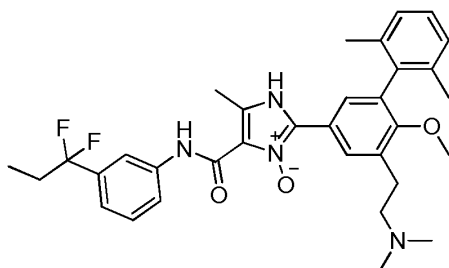


[00808] A mixture of **169-J** (18 mg, 53.8 μ mol, 1.0 eq) and manganese dioxide (46.7 mg, 537 μ mol, 10 eq) in chloroform (6 mL) was stirred at 10°C for 4 hr. The mixture was filtered and filter-cake was rinsed with tetrahydrofuran (10 mL). The filtrate was concentrated under reduced pressure to afford 15 mg (79% yield) of **169-K** as yellow oil.

[00809] LCMS: (ESI) m/z : 312.2 $[M+H]^+$.

[00810] **Step 12: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(5-(2-**
189

(dimethylamino)ethyl)-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (169)

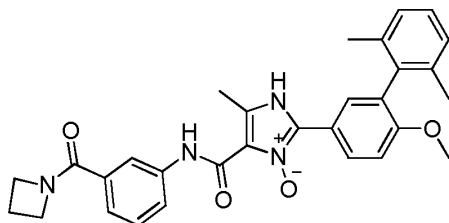


[00811] **169** was obtained *via* similar procedure from **169-K** and **103-G**.

- 5 [00812] **LCMS**: (ESI) m/z : 577.3 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.33 (d, $J = 2.0$ Hz, 1H), 7.93 - 7.82 (m, 2H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.43 (t, $J = 8.0$ Hz, 1H), 7.27 - 7.17 (m, 2H), 7.16 - 7.09 (m, 2H), 3.40 (s, 3H), 3.38 - 3.34 (m, 2H), 3.23 - 3.13 (m, 2H), 2.93 (s, 6H), 2.59 (s, 3H), 2.27 - 2.15 (m, 2H), 2.13 (s, 6H), 0.98 (t, $J = 7.2$ Hz, 3H).

Synthesis of 170

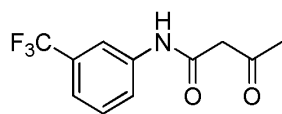
- 10 [00813] **Step 1: Synthesis of 4-((3-(azetidine-1-carbonyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (170)**



- [00814] To a solution of **146-D** (100 mg, 212 μ mol, 1.0 *eq*) in *N,N*-dimethylformamide (2 mL) were added azetidine;hydrochloride (29.8 mg, 318 μ mol, 1.5 *eq*), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (161 mg, 424 μ mol, 2.0 *eq*) and triethylamine (42.9 mg, 424 μ mol, 59.0 μ L, 2.0 *eq*). The mixture was stirred at 50 °C for 3 h. The mixture was filtered and the filtrate was purified by prep-HPLC (trifluoroacetic acid condition. column: Phenomenex Synergi C18 150 x 25 mm x 10 μ m; mobile phase: [water (0.1% trifluoroacetic acid)-acetonitrile]; B%: 47%-77%, 9 min) to give 17.7 mg (16% yield) of **170** as an off-white solid
- 20 [00815] **LCMS**: (ESI) m/z : 511.3 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.32 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.11-8.10 (m, 1H), 7.90 (d, $J = 2.0$ Hz, 1H), 7.72-7.70 (m, 1H), 7.48-7.44 (m, 1H), 7.41-7.39 (m, 1H), 7.32 (d, $J = 8.8$ Hz, 1H), 7.17-7.14 (m, 1H), 7.11-7.09 (m, 2H), 4.42 (t, $J = 8.0$ Hz, 2H), 4.21 (t, $J = 7.6$ Hz, 2H), 3.84 (s, 3H), 2.65 (s, 3H), 2.42-2.34 (m, 2H), 2.01 (s, 6H).

Synthesis of 171

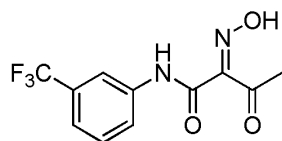
[00816] **Step 1: Synthesis of 3-oxo-N-[3-(trifluoromethyl)phenyl]butanamide (171-A)**



[00817] **171-A** was obtained *via* general procedure from 3-(trifluoromethyl) aniline and 4-methyleneoxetan-2-one.

5 [00818] **LCMS:** (ESI) m/z : 246.0[M+H]⁺.

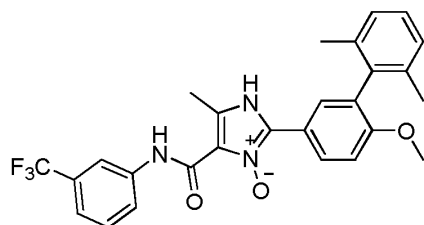
[00819] **Step 2: Synthesis of (2E)-2-hydroxyimino-3-oxo-N-[3-(trifluoromethyl)phenyl]butanamide (171-B)**



[00820] **171-B** was obtained *via* general procedure from **171-A**.

10 [00821] **LCMS:** (ESI) m/z : 274.8[M]⁺.

[00822] **Step 3: Synthesis of 2-[3-(2,6-dimethylphenyl)-4-methoxy-phenyl]-5-methyl-3-oxido-N-[3-(trifluoromethyl)phenyl]-1H-imidazol-3-ium-4-carboxamide (171)**

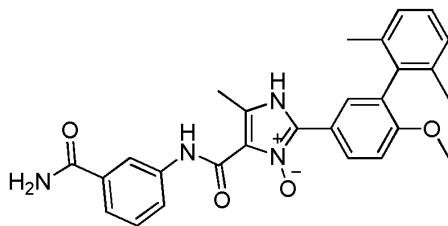


15 [00823] **171** was obtained *via* general procedure from **171-B** and **102-A**.

[00824] **LCMS:** (ESI) m/z : 496.2[M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 8.36 (dd, J = 2.4, 8.8 Hz, 1H), 8.21 (s, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.17-7.13 (m, 1H), 7.11-7.08 (m, 2H), 3.84 (s, 3H), 2.66 (s, 3H), 2.01 (s, 6H).

20 **Synthesis of 172**

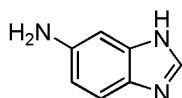
[00825] **Step 1: Synthesis of 4-((3-carbamoylphenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (172)**



- [00826] A mixture of **146-D** (50.0 mg, 106 μmol , 1.0 *eq*) and *N,N*-carbonyldiimidazole (52.0 mg, 318 μmol , 3.0 *eq*) in dichloromethane (2 mL) was stirred at 20 °C for 10 min. Then ammonium hydroxide (17.0 mg, 159 μmol , 1.5 *eq*) was added, and the mixture was stirred at 20 °C for 2 h. The reaction mixture
- 5 was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Phenomenex Gemini-NX C18 75 x 30 mm x 3 μm ; mobile phase: [water (10 mM ammonium bicarbonate)- acetonitrile]; B%: 15%-45%, 8 min) to give 8.7 mg (17% yield) of **172** as a white solid.
- [00827] **LCMS**: (ESI) *m/z*: 471.3 $[\text{M}+\text{H}]^+$. **¹H NMR** (400 MHz, $\text{MeOD-}d_4$) δ : 8.37 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.17 (t, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 2.4 Hz, 1H), 7.87-7.85 (m, 1H), 7.63-7.61 (m, 1H), 7.47-7.44 (m, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.16-7.12 (m, 1H), 7.10-7.08 (m, 2H), 3.83 (s, 3H), 2.64 (s, 3H), 2.02 (s, 6H).
- 10

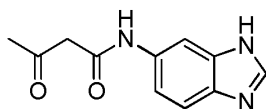
Synthesis of 173

[00828] Step 1: Synthesis of 3H-benzimidazol-5-amine (173-A)

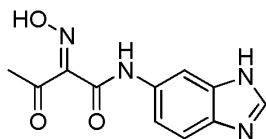


- 15 [00829] The suspension of 6-nitro-1H-benzimidazole (1.00 g, 6.13 mmol, 1.0 *eq*), iron powder (1.71 g, 30.6 mmol, 5.0 *eq*) and ammonium chloride (1.64 g, 30.7 mmol, 5.0 *eq*) in ethanol (20 mL) and water (2 mL) was stirred at 80 °C for 2 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 5/1) to give 500 mg (61% yield) of **173-A** as a yellow solid.
- 20 [00830] **¹H NMR** (400 MHz, $\text{MeOD-}d_4$) δ : 7.93 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.76 (dd, *J* = 2.0, 8.8 Hz, 1H), 3.35 (s, 2H)

[00831] Step 2: Synthesis of *N*-(3H-benzimidazol-5-yl)-3-oxo-butanamide (173-B)



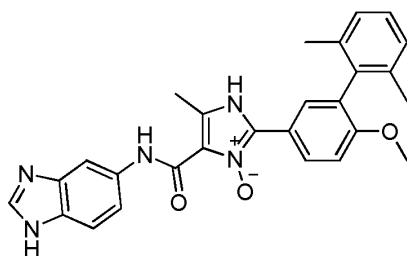
- [00832] **173-B** was obtained *via* general procedure from **173-A**.
- 25 [00833] **LCMS**: (ESI) *m/z*: 218.2 $[\text{M}+\text{H}]^+$.
- [00834] **Step 3: Synthesis of (E)-N-(1H-benzo[d]imidazol-6-yl)-2-(hydroxyimino)-3-**

oxobutanamide (173-C)

[00835] **173-C** was obtained *via* general procedure from **173-B**.

[00836] **LCMS**: (ESI) m/z : 247.1 $[M+H]^+$.

- 5 [00837] **Step 4: Synthesis of 4-((1H-benzo[d]imidazol-5-yl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (173)**

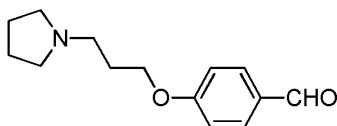


[00838] **173** was obtained *via* general procedure from **173-C** and **102-A**.

- 10 [00839] **LCMS**: (ESI) m/z : 468.1 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 9.31 (s, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.36 (d, J = 11.2 Hz, 1H), 7.99-7.94 (m, 1H), 7.84-7.79 (m, 1H), 7.69-7.64 (m, 1H), 7.35-7.30 (m, 1H), 7.18-7.13 (m, 1H), 7.11-7.08 (m, 2H), 3.85 (s, 3H), 2.70-2.68 (m, 3H), 2.03-2.01 (m, 6H).

Synthesis of 174

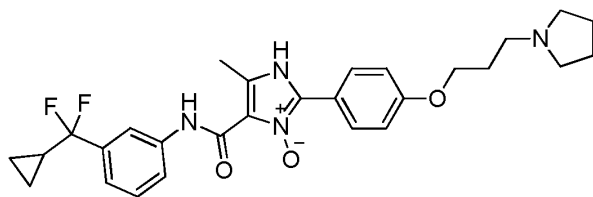
[00840] **Step 1: Synthesis of 4-(3-pyrrolidin-1-ylpropoxy)benzaldehyde (174-A)**



- 15 [00841] To a solution of 4-hydroxybenzaldehyde (200 mg, 1.64 mmol, 1.0 *eq*) in acetonitrile (3 mL) was added potassium carbonate (679 mg, 4.91 mmol, 3.0 *eq*). The mixture was stirred at 80 °C for 1 h. Then potassium iodide (54.4mg, 328 μ mol, 0.20 *eq*) and 1-(3-chloropropyl)pyrrolidine (266 mg, 1.80 mmol, 1.1 *eq*) were added. The mixture was stirred at 80 °C for 6 h. Then the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was
20 purified by silica gel column chromatography (ethyl acetate/ethanol = 1:1) to give 250 mg (65% yield) of **174-A** as a brown oil.

[00842] **¹H NMR** (400 MHz, CDCl₃- d) δ : 9.88 (s, 1H), 7.84-7.80 (m, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.15-4.11 (m, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.62 (s, 4H), 2.12-2.06 (m, 2H), 1.84 (m, 4H).

[00843] **Step 2: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-2-(4-**

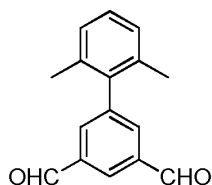
(3-(pyrrolidin-1-yl)propoxy)phenyl)-1*H*-imidazole 3-oxide (174)

[00844] **174** was obtained *via* general procedure from **174-A** and **161-E**.

[00845] **LCMS:** (ESI) *m/z*: 511.2[M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ : 13.7 (s, 1H), 9.80 (s, 1H), 8.40 (d, *J* = 8.8 Hz, 2H), 7.98 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 4.15 (t, *J* = 6.0 Hz, 2H), 3.67-3.55 (m, 2H), 3.38-3.26 (m, 2H), 3.12-3.00 (m, 2H), 2.60 (s, 3H), 2.19-2.10 (m, 2H), 2.08-1.99 (m, 2H), 1.94-1.82 (m, 2H), 1.79-1.61 (m, 1H), 0.76-0.62 (m, 4H).

Synthesis of 175

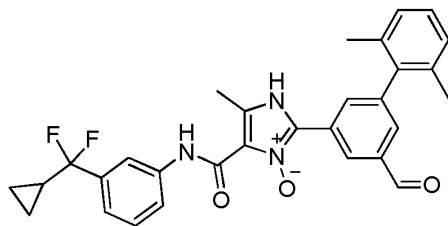
[00846] **Step 1: Synthesis of 2',6'-dimethyl-[1,1'-biphenyl]-3,5-dicarbaldehyde (175-A)**



[00847] A mixture of 5-bromobenzene-1,3-dicarbaldehyde (500 mg, 2.35 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (528 mg, 3.52 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (542 mg, 469 μ mol, 0.20 *eq*), potassium phosphate (996 mg, 4.69 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (10 mL) and water (2 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 440 mg (78% yield) of **175-A** as white solid.

[00848] **¹H NMR** (400 MHz, CDCl₃-*d*) δ : 9.88 (s, 1H), 7.84-7.80 (m, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.15-4.11 (m, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.62 (s, 4H), 2.12-2.06 (m, 2H), 1.84 (m, 4H).

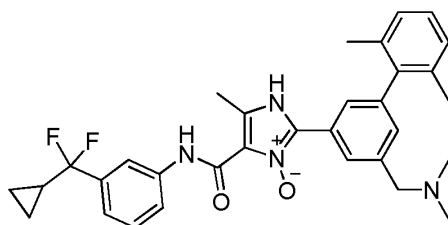
[00849] **Step 2: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(5-formyl-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (175-B)**



[00850] **175-B** was obtained *via* general procedure from **175-A** and **161-E**.

[00851] **LCMS**: (ESI) m/z : 516.2[M+H]⁺.

[00852] **Step 3: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(5-
5 ((dimethylamino)methyl)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide
(175)**

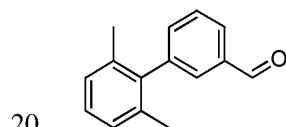


[00853] To a solution of **175-B** (20.0 mg, 38.8 μ mol, 1.0 *eq*) in methanol (2 mL) were added *N*-methylmethanamine;hydrochloride (3.80 mg, 46.6 μ mol, 1.2 *eq*) and sodium cyanoborohydride (24.4
10 mg, 388 μ mol, 10 *eq*). The mixture was stirred at 50 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75*30mm*3 μ m; mobile phase: [water(0.1% trifluoroacetic acid)-acetonitrile];B%: 35%-65%,7 min) to give 11.2 mg (53% yield) of **175** as a white solid.

[00854] **LCMS**: (ESI) m/z : 545.2 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.74 (s, 1H), 7.95-7.91
15 (m, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.50-7.44 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.24-7.20 (m, 1H), 7.18-7.14 (m, 2H), 4.49 (s, 2H), 2.96 (s, 6H), 2.69 (s, 3H), 2.08 (s, 6H), 1.66-1.55 (m, 1H), 0.75-0.68 (m, 4H).

Synthesis of 176

[00855] **Step 1: Synthesis of 2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (176-A)**



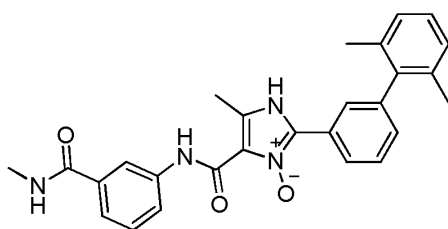
20

[00856] A suspension of 3-bromobenzaldehyde (10.0 g, 54.0 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (9.73 g, 64.8 mmol, 1.2 *eq*), tetrakis(triphenylphosphine)palladium (9.37 g, 8.11 mmol, 0.15 *eq*) and potassium phosphate (34.4 g, 162 mmol, 3.0 *eq*) in 1,2-dimethoxyethane

(200 mL) and water (40 mL) was stirred under nitrogen atmosphere at 100 °C for 12 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with water (100 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0) to give 2.00 g (17% yield) of **176-A** as a yellow oil.

[00857] **¹H NMR** (400 MHz, CDCl₃-*d*) δ: 10.09 (s, 1H), 7.93-7.88 (m, 1H), 7.73-7.70 (m, 1H), 7.67-7.61 (m, 1H), 7.49-7.44 (m, 1H), 7.25-7.20 (m, 1H), 7.18-7.14 (m, 2H), 2.07-2.03 (m, 6H).

[00858] **Step 2: Synthesis of 2-(2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1*H*-imidazole 3-oxide (176)**

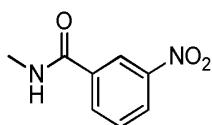


[00859] **176** was obtained *via* general procedure from **176-A** and **177-D**.

[00860] **LCMS**: (ESI) *m/z*: 455.1 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃-*d*) δ: 8.32-8.25 (m, 1H), 8.18-8.04 (m, 2H), 7.88-7.78 (m, 1H), 7.69-7.63 (m, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.47-7.41 (m, 1H), 7.33-7.28 (m, 1H), 7.19-7.14 (m, 1H), 7.14-7.10 (m, 2H), 2.92 (s, 3H), 2.66 (d, *J* = 0.8 Hz, 3H), 2.06 (s, 6H).

Synthesis of 177

[00861] **Step 1: *N*-methyl-3-nitro-benzamide (177-A)**

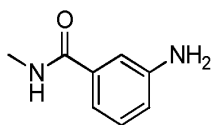


[00862] To a solution of 3-nitrobenzoic acid (15.0 g, 89.8 mmol, 1.0 *eq*) and *N,N*-dimethylformamide (65.6 mg, 897 μmol, 0.010 *eq*) in dichloromethane (150 mL) was added oxalyl dichloride (17.1 g, 134 mmol, 12 mL, 1.5 *eq*) at 0 °C. The mixture was stirred at for 25 °C 40 min under nitrogen atmosphere. Then the reaction mixture was concentrated to give a residue. To the residue was added dichloromethane (150 mL), then methanamine;hydrochloride (7.27 g, 107 mmol, 1.2 *eq*) was added at 0 °C under nitrogen atmosphere. To the reaction was added dropwise triethylamine (27.3 g, 269 mmol, 3.0 *eq*) at 0 °C and the mixture was stirred for 2 h. The reaction was quenched by methanol (20 mL) and then poured into hydrochloric acid (1 M, 200 mL). The precipitate was collected by filtration and dried under reduced pressure to give 4.50 g (28% yield) of **177-A** as a white solid.

[00863] **¹H NMR** (400 MHz, CDCl₃-*d*) δ: 8.59 (t, *J* = 2.0 Hz, 1H), 8.39-8.34 (m, 1H), 8.17 (td, *J* = 1.2,

8.0 Hz, 1H), 7.66 (t, $J = 8.0$ Hz, 1H), 3.07 (d, $J = 4.8$ Hz, 3H).

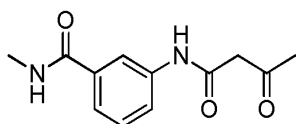
[00864] **Step 2: 3-amino-*N*-methylbenzamide (177-B)**



- [00865] To a solution of **177-A** (4.50 g, 25.0 mmol, 1.0 *eq*) in water (10 mL) and methanol (100 mL) was added iron powder (6.97 g, 124 mmol, 5.0 *eq*) and ammonium chloride (6.68 g, 124 mmol, 5.0 *eq*) at 25 °C. The reaction mixture was heated to 70 °C for 12 h under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by reversed-phase MPLC (0.1% formic acid condition, 0% acetonitrile 20 min) to give 3.0 g (80% yield) of **177-B** as a white solid

- 10 [00866] **LCMS:** (ESI) m/z : 151.1 $[M+H]^+$. **¹H NMR** (400 MHz, DMSO- d_6) δ : 8.16 (d, $J = 4.0$ Hz, 1H), 7.11-6.98 (m, 2H), 6.97-6.88 (m, 1H), 6.80-6.66 (m, 1H), 5.21 (s, 2H), 2.73 (d, $J = 4.4$ Hz, 3H).

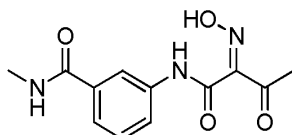
[00867] **Step 3: Synthesis of *N*-methyl-3-(3-oxobutanamido)benzamide (177-C)**



[00868] **177-C** was obtained *via* general procedure from **177-B**.

- 15 [00869] **LCMS:** (ESI) m/z : 235.1 $[M+H]^+$.

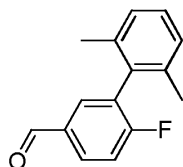
[00870] **Step 4: Synthesis of (Z)-3-(2-(hydroxyimino)-3-oxobutanamido)-*N*-methylbenzamide (177-D)**



[00871] **177-D** was obtained *via* general procedure from **177-C**.

- 20 [00872] **LCMS:** (ESI) m/z : 264.1 $[M+H]^+$.

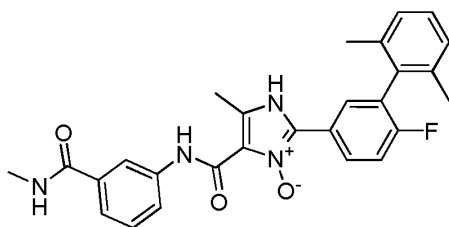
[00873] **Step 5: Synthesis of 6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (177-E)**



[00874] A mixture of 3-bromo-4-fluorobenzaldehyde (200 mg, 1.00 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (227 mg, 1.51 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (581 mg, 503 μ mol, 0.5 *eq*), potassium phosphate (640 mg, 3.02 mmol, 3.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 200 mg (86% yield) of **177-E** as a yellow oil.

10 [00875] ¹H NMR (400 MHz, CDCl₃-d) δ : 10.0 (s, 1H), 7.94 (dd, *J* = 4.8, 8.4 Hz, 1H), 7.74 (dd, *J* = 2.0, 6.8 Hz, 1H), 7.34 (t, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 6.8 Hz, 1H), 7.18-7.12 (m, 2H), 2.06 (s, 6H).

[00876] **Step 6: Synthesis of 2-(6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (177)**

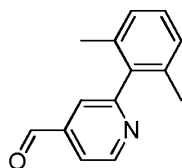


15 [00877] **177** was obtained *via* general procedure from **177-D** and **177-E**

[00878] **LCMS**: (ESI) *m/z*: 473.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 8.36 (dd, *J* = 4.8, 8.8 Hz, 1H), 8.16 (dd, *J* = 2.4, 6.8 Hz, 1H), 8.12 (t, *J* = 1.6 Hz, 1H), 7.87-7.79 (m, 1H), 7.58-7.52 (m, 1H), 7.47-7.38 (m, 2H), 7.24-7.19 (m, 1H), 7.17-7.12 (m, 2H), 2.92 (s, 3H), 2.64 (s, 3H), 2.09 (s, 6H).

Synthesis of 178

20 [00879] **Step 1: Synthesis of 2-(2,6-dimethylphenyl)isonicotinaldehyde (178-A)**

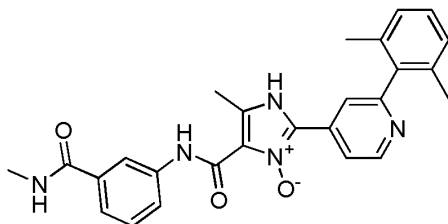


[00880] A mixture of 3-bromo-4-fluorobenzaldehyde (184 mg, 1.00 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (227 mg, 1.51 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (581 mg, 503 μ mol, 0.5 *eq*), potassium phosphate (640 mg, 3.02 mmol, 3.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (1 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed

with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 170 mg (80% yield) of **178-A** as a yellow oil

[00881] **¹H NMR** (400 MHz, CDCl₃-*d*) δ : 10.1 (s, 1H), 8.99 (d, *J* = 4.8 Hz, 1H), 7.71 (dd, *J* = 1.2, 5.2 Hz, 1H), 7.67 (s, 1H), 7.27-7.21 (m, 1H), 7.16-7.12 (m, 2H), 2.05 (s, 6H).

[00882] **Step 2: Synthesis of 2-(2-(2,6-dimethylphenyl)pyridin-4-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1*H*-imidazole 3-oxide (178)**

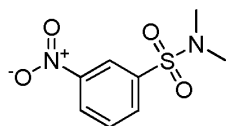


[00883] **178** was obtained *via* general procedure from **177-D** and **178-A**.

10 [00884] **LCMS**: (ESI) *m/z*: 456.1 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.80 (dd, *J* = 1.2, 5.2 Hz, 1H), 8.39-8.34 (m, 2H), 8.14 (t, *J* = 1.6 Hz, 1H), 7.86 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.59-7.54 (m, 1H), 7.48-7.44 (m, 1H), 7.29-7.24 (m, 1H), 7.19-7.16 (m, 2H), 2.94-2.92 (m, 3H), 2.69 (s, 3H), 2.09 (s, 6H).

Synthesis of 179

[00885] **Step 1: Synthesis of *N,N*-dimethyl-3-nitro-benzenesulfonamide (179-A)**



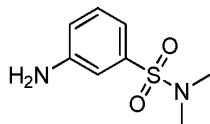
15

[00886] To a solution of 3-nitrobenzenesulfonyl chloride (3.00 g, 13.5 mmol, 1.0 *eq*) and triethylamine (4.80 g, 47.3 mmol, 3.5 *eq*) in dichloromethane (30 mL) was added *N*-methylmethanamine (1.66 g, 20.3 mmol, 1.5 *eq*, hydrochloride) slowly at 0 °C. The mixture was stirred at 25 °C for 1 h and then diluted with saturated sodium carbonate solution (30 mL). The suspension was concentrated under reduced pressure to give an aqueous layer. The aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/1) to give 1.12 g (33% yield) of **179-A** as a white solid.

20 [00887] **¹H NMR** (400 MHz, DMSO-*d*₆) δ : 8.59-8.51 (m, 1H), 8.42-8.33 (m, 1H), 8.23-8.17 (m, 1H), 7.99-7.93 (m, 1H), 2.68 (s, 6H).

25

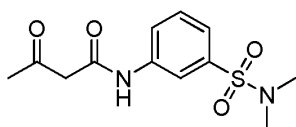
[00888] **Step 2: Synthesis of 3-amino-*N,N*-dimethyl-benzenesulfonamide (179-B)**



- [00889] A suspension of *N,N*-dimethyl-3-nitro-benzenesulfonamide (500 mg, 2.17 mmol, 1.0 *eq*), iron powder (606 mg, 10.8 mmol, 5.0 *eq*) and ammonium chloride (580 mg, 10.8 mmol, 5.0 *eq*) in ethanol (20 mL) and water (2 mL) was stirred at 80 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 5/1) to give 300 mg (68% yield) of **179-B** as a white solid.

[00890] **LCMS:** (ESI) *m/z*: 201.2 [M+H]⁺.

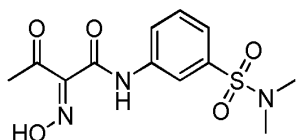
[00891] **Step 3: Synthesis of *N*-(3-(*N,N*-dimethylsulfamoyl)phenyl)-3-oxobutanamide (179-C)**



- [00892] **179-C** was obtained *via* general procedure from **179-B**.

[00893] **LCMS:** (ESI) *m/z*: 285.0 [M+H]⁺.

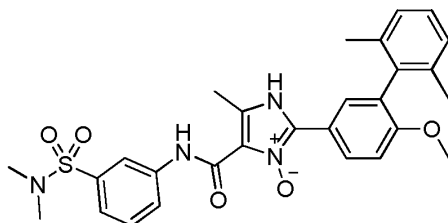
[00894] **Step 4: Synthesis of (*E*)-*N*-(3-(*N,N*-dimethylsulfamoyl)phenyl)-2-(hydroxyimino)-3-oxobutanamide (179-D)**



- [00895] **179-D** was obtained *via* general procedure from **179-C**.

[00896] **LCMS:** (ESI) *m/z*: 314.1 [M+H]⁺.

[00897] **Step 5: Synthesis of 4-((3-(*N,N*-dimethylsulfamoyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (179)**



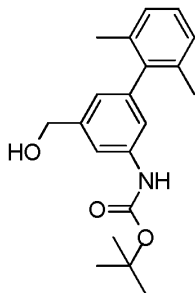
- [00898] **179** was obtained *via* general procedure from **179-D** and **102-A**.

[00899] **LCMS:** (ESI) *m/z*: 535.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ: 8.39-8.32 (m, 2H), 7.95

(d, $J = 2.4$ Hz, 1H), 7.84-7.78 (m, 1H), 7.62-7.56 (m, 1H), 7.52 (s, 1H), 7.29-7.26 (m, 1H), 7.16-7.11 (m, 1H), 7.10-7.07 (m, 2H), 3.82 (s, 3H), 2.72 (s, 6H), 2.62 (s, 3H), 2.02 (s, 6H).

Synthesis of 180

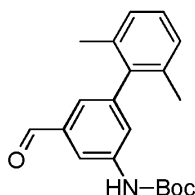
[00900] **Step 1: Synthesis of *tert*-butyl (5-(hydroxymethyl)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)carbamate (180-A)**



[00901] To a solution **147-B** (1.00 g, 2.81 mmol, 1.0 *eq*) in tetrahydrofuran (15 mL) was added lithium borohydride (245 mg, 11.2 mmol, 4.0 *eq*) in three portions at 0 °C. The mixture was stirred at 25 °C for 2 h and then quenched by slow addition of saturated aqueous ammonium chloride (30 mL). The mixture was concentrated under reduced pressure. The resulting aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 470 mg (51% yield) of **180-A** as a colorless oil.

[00902] ¹H NMR (400 MHz, MeOD-*d*₄) δ : 7.42 (s, 1H), 7.10-7.03 (m, 4H), 6.76 (s, 1H), 4.60 (s, 2H), 2.01 (s, 6H), 1.50 (s, 9H).

[00903] **Step 2: Synthesis of *tert*-butyl (5-formyl-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)carbamate (180-B)**

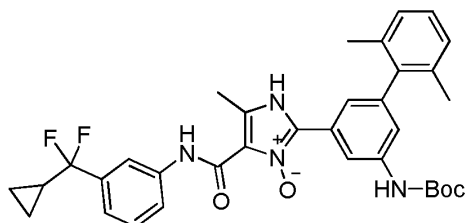


[00904] To a solution of **180-A** (200 mg, 611 μ mol, 1.0 *eq*) in dichloromethane (3 mL) was added Dess-Martin periodinane (310 mg, 733 μ mol, 1.2 *eq*). The mixture was stirred at 25 °C for 30 min and then quenched by slow addition of saturated sodium sulfite solution (15 mL). Then the suspension was separated and the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with saturated sodium bicarbonate solution (15 mL), brine (10 mL), and then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give 180 mg

(91% yield) of **180-B** as a white gum.

[00905] .LCMS: (ESI) m/z : 270.0 [M-56]⁺.

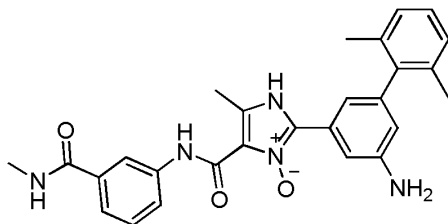
[00906] **Step 3: Synthesis of 2-(5-((tert-butoxycarbonyl)amino)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide 3-oxide (180-C)**



[00907] **180-C** was obtained *via* general procedure from **161-E** and **180-B**.

[00908] LCMS: (ESI) m/z : 570.3 [M+H]⁺.

[00909] **Step 4: Synthesis of 2-(5-amino-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (180)**

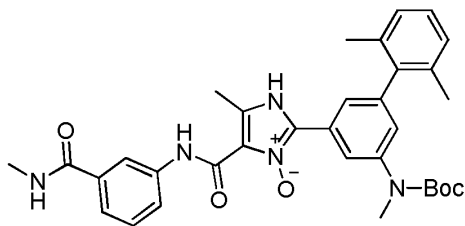


[00910] A solution of **180-C** (120 mg, 211 μ mol, 1.0 *eq*) in hydrogen chloride in ethyl acetate (4 M, 3 mL) was stirred at 25 °C for 30 min. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25mm* 10 μ m; mobile phase: [water (0.1%trifluoroacetic acid) - acetonitrile]; B%: 31%-61%, 10 min) to give desired compound to give 43.4 mg (34% yield) of **180** as an off-white solid.

[00911] LCMS: (ESI) m/z : 470.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 8.34 (t, J = 1.6 Hz, 1H), 8.12 (t, J = 1.6 Hz, 1H), 7.86-7.83 (m, 1H), 7.60-7.55 (m, 2H), 7.47-7.43 (m, 1H), 7.19-7.12 (m, 3H), 7.07-7.04 (m, 1H), 2.93 (s, 3H), 2.67 (s, 3H), 2.08 (s, 6H).

20 **Synthesis of 181**

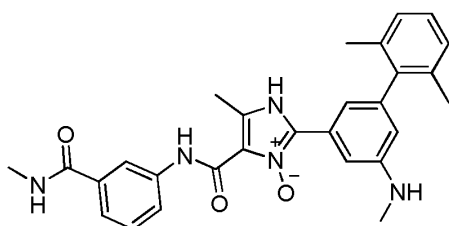
[00912] **Step 1: Synthesis of 2-(5-((tert-butoxycarbonyl)(methyl)amino)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (181-A)**



[00913] **181-A** was obtained *via* general procedure from **177-D** and **147-E**

[00914] **LCMS**: (ESI) m/z : 584.4 $[M+H]^+$.

[00915] **Step 2: Synthesis of 2-(2',6'-dimethyl-5-(methylamino)-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (181)**

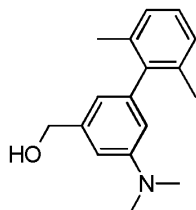


[00916] **181** was obtained *via* similar procedure of **180** from **181-A**.

[00917] **LCMS**: (ESI) m/z : 484.3 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 8.13 (t, J = 1.6 Hz, 1H), 7.91 (t, J = 1.6 Hz, 1H), 7.86-7.84 (m, 1H), 7.58-7.55 (m, 1H), 7.48-7.44 (m, 1H), 7.34 (t, J = 1.6 Hz, 1H), 7.16-7.10 (m, 3H), 6.77-6.76 (m, 1H), 2.96 (s, 3H), 2.93 (s, 3H), 2.67 (s, 3H), 2.09 (s, 6H).

Synthesis of 182

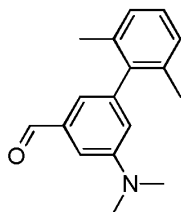
[00918] **Step 1: Synthesis of (5-(dimethylamino)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol (182-A)**



[00919] To a solution of **147-C** (200 mg, 829 μ mol, 1.0 *eq*) and formaldehyde (1 mL, 40% purity) in methanol (5 mL) and acetic acid (0.5 mL) was added sodium cyanoborohydride (312 mg, 4.97 mmol, 6.0 *eq*). The mixture was stirred at 50 °C for 12 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give 200 mg (crude) of **182-A** as a white solid.

[00920] **LCMS**: (ESI) m/z : 256.2 $[M+H]^+$.

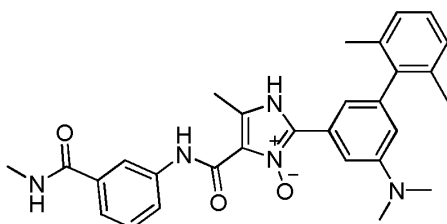
[00921] **Step 2: Synthesis of 5-(dimethylamino)-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (182-B)**



[00922] To a solution of **182-A** (100 mg, 391 μmol , 1.0 *eq*) in dichloromethane (3 mL) was added Dess-Martin periodinane (166 mg, 392 μmol , 1.0 *eq*). The mixture was stirred at 25 °C for 30 min. The mixture was quenched by slow addition of saturated sodium sulfite solution (5 mL). Then the suspension was extracted with ethyl acetate (5 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give 87.0 mg (88% yield) of **182-B** as a white gum.

[00923] **LCMS:** (ESI) m/z : 254.2 $[\text{M}+\text{H}]^+$.

- 10 [00924] **Step 3: Synthesis of 2-(5-(dimethylamino)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (182)**

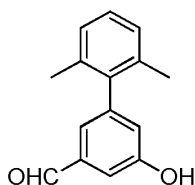


[00925] **182** was obtained *via* general procedure from **177-D** and **182-B**.

- 15 [00926] **LCMS:** (ESI) m/z : 498.3 $[\text{M}+\text{H}]^+$. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.12 (t, J = 1.6 Hz, 1H), 7.97-7.94 (m, 1H), 7.88-7.84 (m, 1H), 7.58-7.55 (m, 1H), 7.47-7.43 (m, 1H), 7.33-7.31 (m, 1H), 7.16-7.09 (m, 3H), 6.79-6.78 (m, 1H), 3.10 (s, 6H), 2.93 (s, 3H), 2.67 (s, 3H), 2.09 (s, 6H).

Synthesis of 183

[00927] **Step 1: Synthesis of 5-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (183-A)**

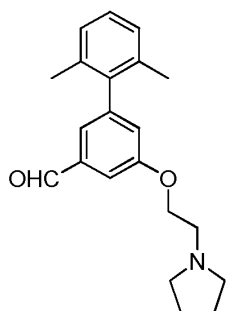


- 20 [00928] A mixture of 3-bromo-4-methoxy-benzaldehyde (400 mg, 2.00 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (450 mg, 3.00 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (580 mg, 500 μmol , 0.25 *eq*), potassium phosphate (850 mg, 4 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (10

mL) and water (2 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 30/1) to give 340 mg (75% yield) of **183-A** as colourless oil.

[00929] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.94 (s, 1H), 7.25 (dd, *J* = 1.2, 2.4 Hz, 1H), 7.20-7.15 (m, 1H), 7.14-7.10 (m, 3H), 6.85 (dd, *J* = 1.6, 2.4 Hz, 1H), 1.98 (s, 6H).

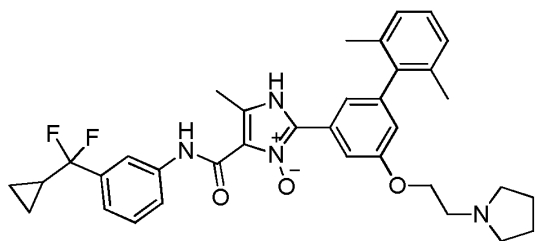
[00930] **Step 2: Synthesis of 2',6'-dimethyl-5-(2-(pyrrolidin-1-yl)ethoxy)-[1,1'-biphenyl]-3-carbaldehyde (183-B)**



[00931] To a solution of **183-A** (200 mg, 883 μmol, 1.0 eq) in acetonitrile (3 mL) was added potassium carbonate (366 mg, 2.65 mmol, 3.0 eq). The mixture was stirred at 80 °C for 1 h, then potassium iodide (29.3 mg, 176 μmol, 0.2 eq) and 1-(2-chloroethyl)pyrrolidine;hydrochloride (165 mg, 972 μmol, 1.1 eq) were added. The mixture was stirred at 80 °C for further 6 h. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (ethyl acetate/ethanol = 1:1) to give 180 mg (63% yield) of **183-B** as a brown oil.

[00932] ¹H NMR (400 MHz, CDCl₃-*d*) δ: 9.99 (s, 1H), 7.41 (dd, *J* = 1.6, 2.4 Hz, 1H), 7.25-7.10 (m, 4H), 7.02 (dd, *J* = 1.6, 2.4 Hz, 1H), 4.23 (t, *J* = 5.6 Hz, 2H), 3.00 (t, *J* = 5.6 Hz, 2H), 2.72 (s, 4H), 2.04 (s, 6H), 1.88-1.84 (m, 4H).

[00933] **Step 3: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(2',6'-dimethyl-5-(2-(pyrrolidin-1-yl)ethoxy)-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (183)**

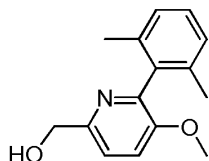


[00934] **183** was obtained *via* general procedure from **183-B** and **161-E**.

[00935] **LCMS**: (ESI) m/z : 601.4[M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.12 (dd, J = 1.6, 2.4 Hz, 1H), 7.93 (s, 1H), 7.75-7.70 (m, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.16-7.12 (m, 1H), 7.11-7.08 (m, 2H), 6.80 (dd, J = 1.6, 2.4 Hz, 1H), 4.44-4.38 (m, 2H), 3.58-3.53 (m, 2H), 3.35 (t, J = 6.8 Hz, 4H), 2.56 (s, 3H), 2.10-2.05 (m, 10H), 1.65-1.55 (m, 1H), 0.74-0.68 (m, 4H).

Synthesis of 186

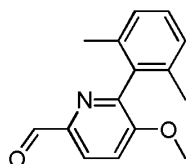
[00936] **Step 1: Synthesis of (6-(2,6-dimethylphenyl)-5-methoxypyridin-2-yl)methanol (186-A)**



[00937] To a solution of **149-B** in tetrahydrofuran (2 mL) was added lithium borohydride (55.2 mg, 2.54 mmol, 4.0 *eq*). The reaction mixture was stirred at 25 °C for 2 h under nitrogen atmosphere and then quenched by saturated ammonium chloride solution (10 mL). It was extracted with ethyl acetate (15 mL x 2). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 150 mg (crude) of **186-A** as a black oil.

[00938] **LCMS**: (ESI) m/z : 244.1[M+H]⁺.

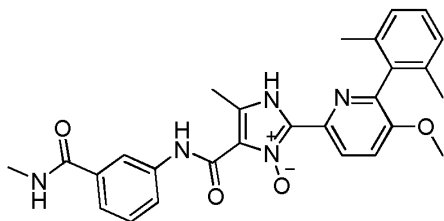
[00939] **Step 2: Synthesis of 6-(2,6-dimethylphenyl)-5-methoxypicolinaldehyde (186-B)**



[00940] To a solution of **186-A** (0.15 g, 616 μ mol, 1.0 *eq*) in dichloroethane (2 mL) was added Dess-Martin periodinane (392 mg, 924 μ mol, 1.5 *eq*). The reaction mixture was stirred at 25 °C for 2 h. The reaction suspension was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 5/1 to 3/1) to give 140 mg (94% yield) of **186-B** as a yellow solid.

[00941] **LCMS**: (ESI) m/z : 242.1 [M+H]⁺.

[00942] **Step 3: Synthesis of 2-(6-(2,6-dimethylphenyl)-5-methoxypyridin-2-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (186)**

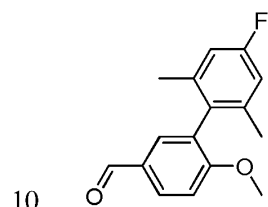


[00943] **186** was obtained *via* general procedure from **186-B** and **177-D**.

[00944] **LCMS**: (ESI) m/z : 486.3 $[M+H]^+$. **1H NMR** (400 MHz, DMSO- d_6) δ : 13.59 (s, 1H), 13.30 (s, 1H), 9.15 (d, $J = 8.8$ Hz, 1H), 8.54-8.44 (m, 1H), 8.06 (s, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.80-7.73 (m, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.47-7.40 (m, 1H), 7.23-7.17 (m, 1H), 7.15-7.09 (m, 2H), 3.84 (s, 3H), 2.80 (d, $J = 4.4$ Hz, 3H), 2.55 (s, 3H), 1.96 (s, 6H).

Synthesis of 185

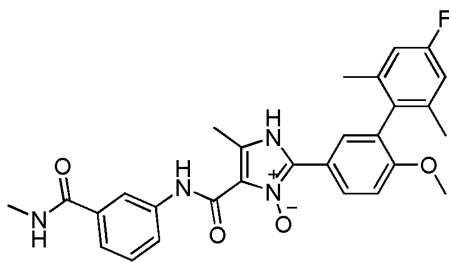
[00945] **Step 1: Synthesis of 4'-fluoro-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (185-A)**



[00946] A mixture of **209-A** (100 mg, 555 μ mol, 1.0 *eq*), 2-bromo-5-fluoro-1,3-dimethyl-benzene (124 mg, 611 μ mol, 1.1 *eq*), potassium phosphate (236 mg, 1.11 mmol, 2.0 *eq*), tetrakis(triphenylphosphine)palladium (160 mg, 139 μ mol, 0.25 *eq*) in 1,2-dimethoxyethane (3 mL) and water (0.5 mL) was degassed and purged with nitrogen for 3 times. Then the mixture was stirred at 100 °C for 16 h under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with Ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 50 mg (35% yield) of **185-A** as a yellow solid.

[00947] **LCMS**: (ESI) m/z : 259.1 $[M+H]^+$.

[00948] **Step 2: Synthesis of 2-(4'-fluoro-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (185)**

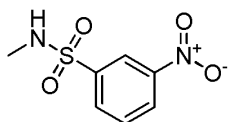


[00949] **185** was obtained *via* general procedure from **185-A** and **177-D**.

[00950] **LCMS**: (ESI) m/z : 503.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.36 (dd, J = 2.4, 8.8 Hz, 1H), 8.12 (t, J = 1.6 Hz, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.85-7.82 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.47-7.43 (m, 1H), 7.30 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 9.6 Hz, 2H), 3.84 (s, 3H), 2.93 (s, 3H), 2.65 (s, 3H), 2.02 (s, 6H).

Synthesis of 187

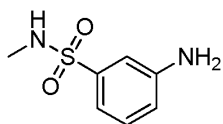
[00951] Step 1: Synthesis of *N*-methyl-3-nitrobenzenesulfonamide (**187-A**)



[00952] To a solution of 3-nitrobenzenesulfonyl chloride (2.00 g, 9.02 mmol, 1.0 *eq*) and triethylamine (3.20 g, 31.5 mmol, 3.5 *eq*) in dichloromethane (20 mL) was added methanamine (913 mg, 13.5 mmol, 1.5 *eq*, hydrochloric acid) slowly at 0 °C. The mixture was stirred at 25 °C for 1 hr. To the mixture was added saturated sodium carbonate solution (20 mL), and concentrated under reduced pressure to give a aqueous layer. The aqueous layer was extracted with ethyl acetate (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 5/1 to 3/1) to give 640 mg (32% yield) of **187-A** as a white solid.

[00953] **1H NMR** (400 MHz, $CDCl_3-d$) δ : 8.75-8.70 (m, 1H), 8.49-8.42 (m, 1H), 8.24-8.18 (m, 1H), 7.81-7.74 (m, 1H), 4.51 (s, 1H), 2.78 (s, 3H)

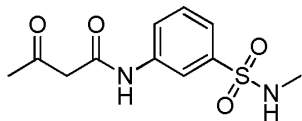
[00954] Step 2: Synthesis of 3-amino-*N*-methylbenzenesulfonamide (**187-B**)



[00955] A suspension of **187-A** (500 mg, 2.17 mmol, 1.0 *eq*), iron powder (606 mg, 10.8 mmol, 5.0 *eq*) and ammonium chloride (580 mg, 10.8 mmol, 5.0 *eq*) in ethanol (20 mL) and water (2 mL) was stirred at 80 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 5/1) to give 300 mg (68% yield) of **187-B** as a white solid.

[00956] ^1H NMR (400 MHz, CDCl_3 - d) δ : 7.29-7.24 (m, 1H), 7.22-7.13 (m, 2H), 6.88-6.82 (m, 1H), 4.52-4.51 (m, 1H), 3.91 (s, 2H), 2.65 (s, 3H).

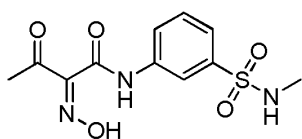
[00957] **Step 3: Synthesis of *N*-(3-(*N*-methylsulfamoyl)phenyl)-3-oxobutanamide (187-C)**



5 [00958] **187-C** was obtained *via* general procedure from **187-B**.

LCMS: (ESI) m/z : 271.0 $[\text{M}+\text{H}]^+$.

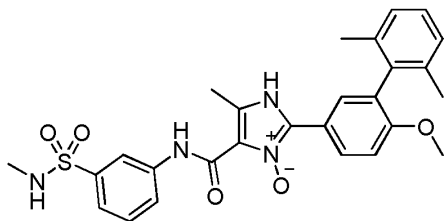
[00959] **Step 4: Synthesis of (Z)-2-(hydroxyimino)-*N*-(3-(*N*-methylsulfamoyl)phenyl)-3-oxobutanamide (187-D)**



10 [00960] **187-D** was obtained *via* general procedure from **187-C**.

[00961] **LCMS:** (ESI) m/z : 300.0 $[\text{M}+\text{H}]^+$.

[00962] **Step 5: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(*N*-methylsulfamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (193)**

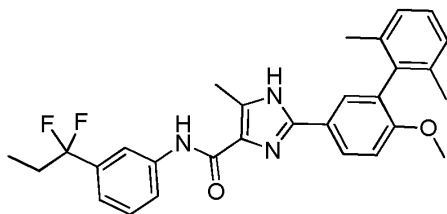


15 [00963] **187** was obtained *via* general procedure from **187-D** and **102-A**.

[00964] **LCMS:** (ESI) m/z : 521.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ : 8.37 (dd, $J = 2.4, 8.8$ Hz, 1H), 8.34-8.32 (m, 1H), 7.92 (d, $J = 2.4$ Hz, 1H), 7.85-7.81 (m, 1H), 7.59-7.55 (m, 2H), 7.32 (d, $J = 8.8$ Hz, 1H), 7.16-7.13 (m, 1H), 7.11-7.08 (m, 2H), 3.84 (s, 3H), 2.66 (s, 3H), 2.56 (s, 3H), 2.02 (s, 6H).

Synthesis of 188

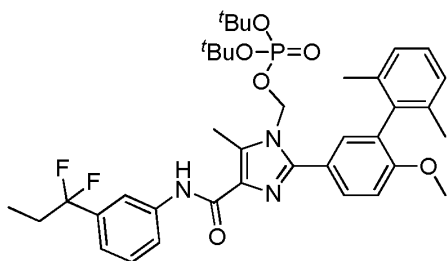
20 [00965] **Step 1: Synthesis of *N*-(3-(1,1-difluoropropyl)phenyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole-4-carboxamide (188-A)**



[00966] To a solution of **101** (300 mg, 593 μmol , 1.0 *eq*) in methanol (50 mL) was added Pd/C (60.0 mg, 10% purity). The reaction mixture was stirred at 25 °C for 2 h under hydrogen atmosphere (15 psi). The reaction suspension was filtered to remove the catalyst and the filtrate was concentrated under reduced pressure to give 250 mg (65% yield) of **188-A** as a light yellow solid.

[00967] LCMS: (ESI) m/z : 490.0 $[\text{M}+\text{H}]^+$.

[00968] **Step 2: Synthesis of di-tert-butyl ((4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazol-1-yl)methyl) phosphate (188-B)**



10

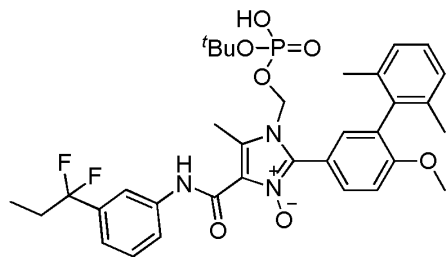
[00969] To a solution of **188-A** (100 mg, 175 μmol , 1.0 *eq*) and di-tert-butyl chloromethyl phosphate (49.9 mg, 193 μmol , 1.1 *eq*) in *N,N*-dimethylformamide (2 mL) was added cesium carbonate (62.9 mg, 193 μmol , 1.1 *eq*). The mixture was stirred at 50 °C for 12 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Phenomenex Luna C18 150*25mm* 10 μm ; mobile phase: [water(0.2%FA)-ACN]; B%: 70%-100%, 10min) to give 60.0 mg (44% yield) of **188-B** as a colorless oil.

15

[00970] LCMS: (ESI) m/z : 711.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3-d) δ : 9.28 (s, 1H), 7.87-7.67 (m, 3H), 7.50 (d, J = 2.0 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.23-7.15 (m, 2H), 7.12 (d, J = 8.0 Hz, 3H), 5.73 (d, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.83 (s, 3H), 2.26-2.10 (m, 2H), 2.07 (s, 6H), 1.43 (s, 18H), 1.00 (t, J = 7.6 Hz, 3H).

20

[00971] **Step 3: Synthesis of 1-(((tert-butoxy(hydroxy)phosphoryl)oxy)methyl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (188)**

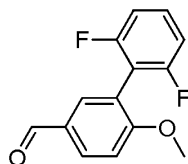


[00972] To a solution of **188-B** (10.0 mg, 13.0 μmol , 1.0 *eq*) in dichloromethane (2 mL) was added 3-chlorobenzoperoxoic acid (2.92 mg, 14.3 μmol , 1.1 *eq*). The mixture was stirred at 25 °C for 12 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3 μm ; mobile phase: [water(0.225%FA)-ACN];B%: 65%-95%,10min) and (column: Phenomenex Gemini-NX C18 75*30mm*3 μm ;mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN];B%: 57%-87%,7min) to give 5.5 mg (55% yield) of **188** as a white solid.

[00973] **LCMS**: (ESI) *m/z*: 672.2 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, CDCl_3 -*d*) δ : 12.99 (br s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.85-7.70 (m, 2H), 7.62-7.51 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.25-7.11 (m, 3H), 7.10-7.02 (m, 2H), 5.80-5.41 (m, 2H), 3.79 (s, 3H), 2.84 (s, 3H), 2.31-2.07 (m, 2H), 2.03 (s, 6H), 1.24 (br s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H).

Synthesis of 184

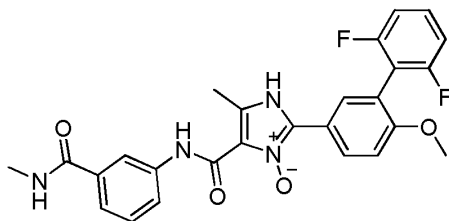
[00974] **Step 1: Synthesis of 2',6'-difluoro-6-methoxy-[1,1'-biphenyl]-3-carbaldehyde (184-A)**



[00975] A mixture of (5-formyl-2-methoxy-phenyl)boronic acid (50 mg, 278 μmol , 1.0 *eq*), 2-bromo-1,3-difluoro-benzene (54 mg, 278 μmol , 1.0 *eq*), potassium phosphate (118 mg, 555 μmol , 2.0 *eq*), tetrakis(triphenylphosphine)palladium (80 mg, 69.5 μmol , 0.25 *eq*) in 1,2-dimethoxyethane (1 mL) and water (0.1 mL) was stirred at 100 °C for 16 h under nitrogen atmosphere. The mixture filtered and the filter was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/1) to give 50 mg (72% yield) of **184-A** as a yellow solid.

[00976] **^1H NMR** (400 MHz, CDCl_3 -*d*) δ : 9.94 (s, 1H), 7.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.83 (d, *J* = 2.0, 1H), 7.37 - 7.33 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.01-6.97 (m, 2H), 3.90 (s, 3H).

[00977] **Step 2: Synthesis of 2-(2',6'-difluoro-6-methoxy-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(methylcarbamoyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (184)**

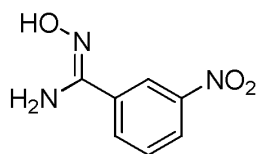


[00978] **184** was obtained *via* general procedure from **184-A** and **177-D**.

[00979] **LCMS**: (ESI) m/z : 493.3 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 8.39 (dd, J = 8.8, 2.0 Hz, 1H), 8.21 (d, J = 2.4 Hz, 1H), 8.12 (t, J = 1.6 Hz, 1H), 7.86-7.83 (m, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.47-7.42 (m, 2H), 7.33 (d, J = 8.8 Hz, 1H), 7.08-7.04 (m, 2H), 3.89 (s, 3H), 2.93 (s, 3H), 2.67 (s, 3H).

Synthesis of 190

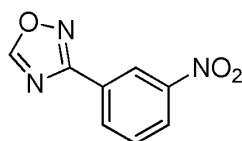
[00980] **Step 1: Synthesis of (Z)-N'-hydroxy-3-nitrobenzimidamide (190-A)**



[00981] To a solution of 3-nitrobenzonitrile (5.0 g, 33.7 mmol, 1.0 *eq*) in ethanol (50 mL) were added a solution of hydroxylamine hydrochloride (2.4 g, 33.7 mmol, 1.0 *eq*) in water (5 mL), followed by the addition of sodium carbonate (1.8 g, 16.8 mmol, 0.5 *eq*) in water (5 mL). The mixture was stirred at 20 °C for 12 hr. The suspension was filtered and the filter cake was washed with water (50 mL). The filter cake was triturated with petroleum ether (30 mL) at 20 °C for 5 min. After filtration, the filter cake was dried under reduced pressure to give 5.1 g (83% yield) of **190-A** as a yellow solid.

[00982] **¹H NMR** (400 MHz, DMSO- d_6) δ : 9.97 (s, 1H), 8.51 (t, J = 1.6 Hz, 1H), 8.23-8.21 (m, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 6.09 (s, 2H).

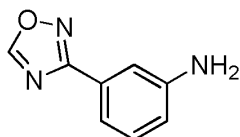
[00983] **Step 2: 3-(3-nitrophenyl)-1,2,4-oxadiazole (190-B)**



[00984] To a solution of **190-A** (2.00 g, 11.0 mmol, 1.0 *eq*) in triethyl orthoformate (20 mL) was added boron trifluoride diethyl ether (156 mg, 1.10 mmol, 0.1 *eq*). The mixture was stirred at 20 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with petroleum ether (50 mL) at 20 °C for 5 min. After filtration, the filter cake was dried under reduced pressure to give 1.2 g (56% yield) of **190-B** as a yellow solid.

[00985] **¹H NMR** (400 MHz, MeOD- d_4) δ = 9.38 (s, 1H), 8.88 (s, 1H), 8.48 (d, J = 7.6 Hz, 1H), 8.42 (d, J = 7.6 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H).

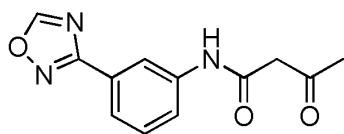
[00986] **Step 3: Synthesis of 3-(1,2,4-oxadiazol-3-yl)aniline (190-C)**



[00987] To a solution of **190-B** (600 mg, 3.14 mmol, 1 eq) in ethanol (6 mL) was added tin(II) dichloride dihydrate (3.54 g, 15.70 mmol, 5 eq). The mixture was stirred at 20 °C for 16 hr. The mixture was added
5 to aqueous potassium fluoride (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 500 mg (98% yield) of **190-C** as a yellow solid.

[00988] **LCMS:** (ESI) m/z : 162.0 $[M+H]^+$.

[00989] **Step 4: Synthesis of N-(3-(1,2,4-oxadiazol-3-yl)phenyl)-3-oxobutanamide (190-D)**

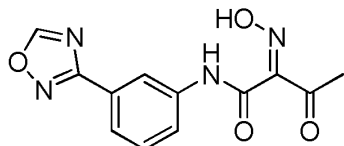


10

[00990] **190-D** was obtained *via* general procedure from **190-C**.

LCMS: (ESI) m/z : 245.9 $[M+H]^+$.

[00991] **Step 5: Synthesis of Z)-N-(3-(1,2,4-oxadiazol-3-yl)phenyl)-2-(hydroxyimino)-3-oxobutanamide (190-E)**

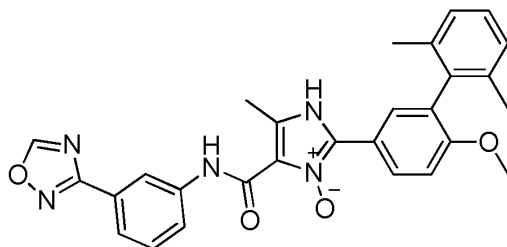


15

[00992] **190-E** was obtained *via* general procedure from **190-D**.

[00993] **LCMS:** (ESI) m/z : 275.1 $[M+H]^+$.

[00994] **Step 6: Synthesis of 4-((3-(1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (190)**



20

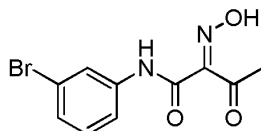
[00995] **190** was obtained *via* general procedure from **190-E** and **102-A**.

[00996] **LCMS:** (ESI) m/z : 496.3 $[M+H]^+$. **¹H NMR** (400 MHz, DMSO- d_6) δ : 13.82 (s, 1H), 13.17 (s,

1H), 9.73 (d, $J = 1.2$ Hz, 1H), 8.57-8.56 (m, 2H), 8.12 (s, 1H), 7.75 (t, $J = 6.4$ Hz, 2H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 7.20-7.16 (m, 1H), 7.14-7.12 (m, 2H), 3.79 (s, 3H), 2.59 (s, 3H), 1.97 (s, 6H).

Synthesis of 191

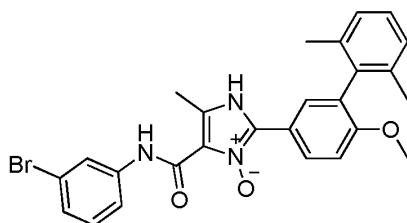
- 5 [00997] **Step 1: Synthesis of (2E)-N-(3-bromophenyl)-2-hydroxyimino-3-oxo-butanamide (191-A)**



191-A was obtained *via* general procedure from 3-bromoaniline.

[00998] **LCMS:** (ESI) m/z : 284.9 $[M+H]^+$. **1H NMR** (400 MHz, $CDCl_3-d$) δ : 11.06 (br s, 1H), 7.90 (br s, 1H), 7.61-7.26 (m, 4H), 2.61 (s, 3H).

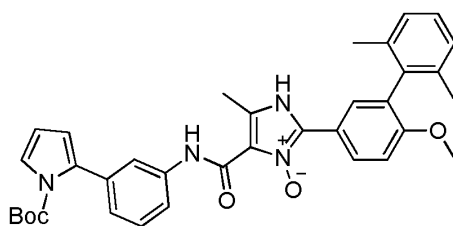
- 10 [00999] **Step 2: Synthesis of 4-((3-bromophenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (191-B)**



[001000] **191-B** was obtained *via* general procedure from **191-A** and **102-A**.

[001001] **LCMS:** (ESI) m/z : 506.1 $[M+H]^+$.

- 15 [001002] **Step 3: Synthesis of 4-((3-(1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (191-C)**



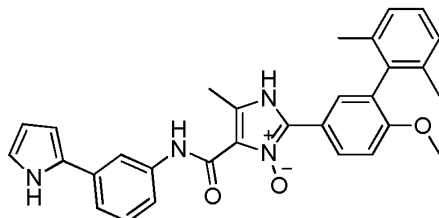
- 20 [001003] A mixture of **191-B** (260 mg, 462 μ mol, 1.0 *eq*), (1-tert-butoxycarbonylpyrrol-2-yl)boronic acid (184 mg, 873 μ mol, 1.9 *eq*), tetrakis(triphenylphosphine)palladium (25.2 mg, 21.8 μ mol, 0.05 *eq*) and potassium carbonate (120 mg, 873 μ mol, 1.9 *eq*) in dioxane (6 mL) and water (1 mL) was stirred at 80°C for 14 hr. The mixture was concentrated and the residue was diluted with water (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layer was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25

mm* 10 um; mobile phase: [water (0.1%TFA)-ACN]; B%: 65%-95%, 10 min) to give 80 mg (28.6% yield) of **191-C** as green solid.

[001004] LCMS: (ESI) m/z : 593.3 $[M+H]^+$.

[001005] **Step 4: Synthesis of 4-((3-(1H-pyrrol-2-yl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-**

5 **dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (191)**

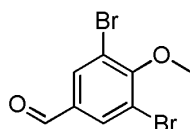


[001006] To a suspension of **191-C** (40 mg, 75.6 μ mol, 1.0 *eq*) in water (4 mL) was added trifluoroacetic acid (4 mL). The suspension was stirred at 15°C for 1 hr. The solution was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 10 150*25 mm* 10 um; mobile phase :[water (0.1%TFA)-ACN]; B%: 50%-80%, 10 min) to give 12.1 mg (30% yield) of **191** as a brown solid.

[001007] LCMS: (ESI) m/z : 493.5 $[M+H]^+$. ^1H NMR (400 MHz, MeOD- d_4) δ : 10.88 (br s, 1H), 8.49 (t, J = 1.6 Hz, 1H), 8.39-8.27 (m, 1H), 8.18-8.09 (m, 1H), 7.99 (dd, J = 2.4, 8.8 Hz, 1H), 7.89-7.77 (m, 1H), 7.75-7.65 (m, 1H), 7.55 (td, J = 2.0, 7.2 Hz, 1H), 7.42-7.28 (m, 2H), 7.17-7.05 (m, 3H), 6.47 (t, J = 2.8 Hz, 1H), 6.15 (t, J = 2.8 Hz, 1H), 3.87-3.80 (m, 3H), 2.67 (d, J = 3.2 Hz, 3H), 2.01 (d, J = 2.8 Hz, 6H).

Synthesis of 192

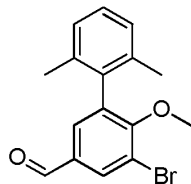
[001008] **Step 1: Synthesis of 3,5-dibromo-4-methoxybenzaldehyde (192-A)**



[001009] To a solution of 3,5-dibromo-4-hydroxy-benzaldehyde (18.0 g, 64.3 mmol, 1.0 *eq*) in dimethyl formamide (200 mL) were added potassium carbonate (11.6 g, 83.6 mmol, 1.3 *eq*) and iodomethane (13.7 g, 96.5 mmol, 1.5 *eq*). The mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove dimethyl formamide. The residue was diluted with ammonium chloride (100 mL) and water (150 mL), and then extracted with ethyl acetate (200 mL x 3). 20 The combined organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with solvent (petroleum ether/ ethyl acetate = 5/1) at 20 °C for 30 min. Then the mixture was filtered and the filter cake was dried under reduced pressure to give 11.2 g (59% yield) of **192-A** as an off-white solid.

[001010] ¹H NMR (400 MHz, CDCl₃-d) δ: 9.87 (s, 1H), 8.04 (s, 2H), 3.97 (s, 3H).

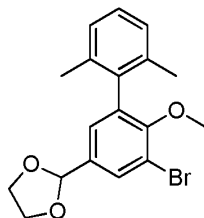
[001011] **Step 2: Synthesis of 5-bromo-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (192-B)**



5 [001012] A mixture of **192-A** (5.00 g, 17.01 mmol, 1 *eq*), (2,6-dimethylphenyl)boronic acid (5.10 g, 34.0 mmol, 2.0 *eq*), potassium phosphate (7.22 g, 34.0 mmol, 2.0 *eq*), tetrakis(triphenylphosphine)palladium (1.18 g, 1.02 mmol, 0.06 *eq*) in water (10 mL) and dioxane (60 mL) was degassed and purged with nitrogen for 3 times. Then the mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50/1) to give 4.40 g (81% yield) of **192-B** as a colorless oil.

15 [001013] ¹H NMR (400 MHz, CDCl₃-d) δ: 9.92 (s, 1H), 8.04 (s, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.26-7.22 (m, 1H), 7.16-7.13 (d, *J* = 7.6 Hz, 2H), 3.49 (s, 3H), 2.08 (s, 6H).

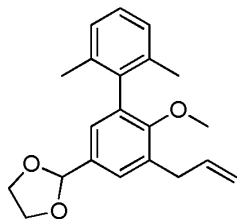
[001014] **Step 3: 2-(5-bromo-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-1,3-dioxolane (192-C)**



20 [001015] To a solution of **192-B** (4.40 g, 13.8 mmol, 1.0 *eq*) and ethylene glycol (17.1 g, 276 mmol, 20.0 *eq*) in toluene (60 mL) was added *p*-toluenesulfonic acid (2.37 g, 13.8 mmol, 1.0 *eq*). The mixture was stirred at 135 °C for 16 h. The reaction mixture was diluted with saturated sodium bicarbonate solution (80 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2.40 g (60% yield) of **192-C** as a yellow oil.

25 [001016] ¹H NMR (400 MHz, CDCl₃-d) δ: 7.72 (d, *J* = 2.0 Hz, 1H), 7.21-7.10 (m, 4H), 5.77 (s, 1H), 4.14-4.11 (m, 2H), 4.05-4.03 (m, 2H), 3.43 (s, 3H), 2.07 (s, 6H).

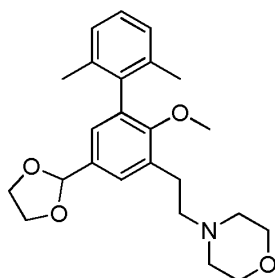
[001017] **Step 4: 2-(5-allyl-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-1,3-dioxolane (192-D)**



[001018] To a solution of **192-C** (1.60 g, 4.40 mmol, 1.0 *eq*), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.48 g, 8.81 mmol, 2.0 *eq*), tetrakis[triphenylphosphine]palladium (1.02 g, 881 μ mol, 0.2 *eq*) in water (4 mL) and dimethoxyethane (20 mL) was added potassium phosphate (1.87 g, 8.81 mmol, 2.0 *eq*). The mixture was stirred at 100 °C for 6 h at nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (300 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum/ethyl acetate = 5/1) to give 1.30 g (91% yield) of **192-D** as a colorless oil.

10 [001019] **LCMS:** (ESI) *m/z*: 325.1 [M+H]⁺.

[001020] **Step 5: 4-(2-(5-(1,3-dioxolan-2-yl)-2-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)ethyl)morpholine (192-E)**

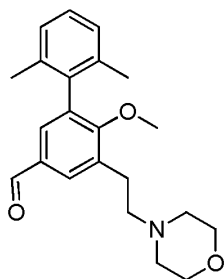


[001021] Ozone (15Psi) was bubbled into a solution of **192-D** (700 mg, 2.16mmol, 1.0 *eq*) in DCM (20 mL) at -78 °C for 0.5 h. After the excess ozone was purged by nitrogen, triphenylphosphine (566 mg, 2.16 mmol, 1.0 *eq*) was added. Then morpholine (188 mg, 2.16 mmol, 1.0 *eq*) and sodium cyanoborohydride (1.36 g, 21.6 mmol, 10.0 *eq*) were added to the mixture at 20 °C. The mixture was stirred at 20 °C for 1.5 h. The reaction mixture was quenched by addition of water (30 mL), and then extracted with dichloromethane (30 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 100 mg (12% yield) of **192-E** as a colorless oil.

[001022] **LCMS:** (ESI) *m/z*: 398.2[M+H]⁺.

[001023] **Step 6: 6-methoxy-2',6'-dimethyl-5-(2-morpholinoethyl)-[1,1'-biphenyl]-3-carbaldehyde (192-F)**

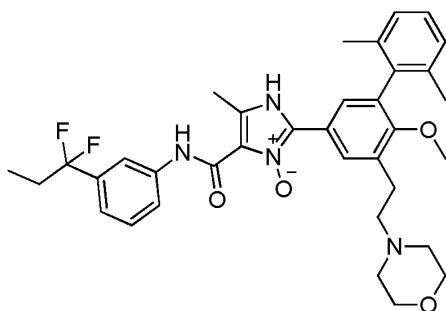
25



[001024] A solution of **192-E** (100 mg, 252 μmol , 1.0 *eq*) in hydrogen chloride in ethyl acetate (4 M, 3 mL) was stirred at 25 °C for 30 min. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25mm*
 5 10 μm ; mobile phase:[water(0.1% trifluoroacetic acid)- acetonitrile]; B%: 26%-56%,10min) to give 30.0 mg (34% yield) of **192-F** as a colorless oil.

[001025] **LCMS:** (ESI) m/z : 354.1 $[\text{M}+\text{H}]^+$.

[001026] **Step 7: 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-5-(2-morpholinoethyl)-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (192)**



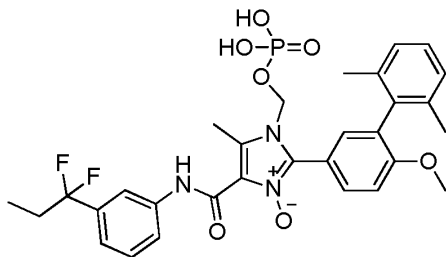
10

[001027] **192** was obtained via general procedure from **103-G** and **192-F**.

[001028] **LCMS:** (ESI) m/z : 619.2 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 8.26 (d, J = 2.4 Hz, 1H), 7.91 (s, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.21-7.17 (m, 1H), 7.16-7.12 (m, 2H), 3.78-3.74 (m, 4H), 3.38 (s, 3H), 3.04-2.99 (m, 2H), 2.80-2.75 (m, 2H), 2.68 (s, 4H), 2.62 (s, 3H), 2.24-2.15 (m, 2H), 2.13 (s, 6H), 0.98 (t, J = 7.6 Hz, 3H).
 15

Synthesis of 193

[001029] **Step 1: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1-((phosphonooxy)methyl)-1H-imidazole 3-oxide (193)**
 20

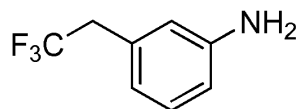


[001030] A solution of **188** (40 mg, 42 μ mol, 1.0 *eq*) in dichloromethane (2 mL) and formic acid (0.5 mL) was stirred at 25 °C for 12 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Waters Xbridge 150*25mm* 5 μ m;
 5 mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 3%-33%, 9min) to give 20.4 mg (78% yield) of **193** as a white solid.

[001031] **LCMS:** (ESI) *m/z*: 616.0 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 7.98 (d, *J* = 8.8 Hz, 1H), 7.89 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.05-7.18 (m, 3H), 5.70 (d, *J* = 6.4 Hz, 2H), 3.86 (s, 3H),
 10 2.93 (s, 3H), 2.25 - 2.15 (m, 2H), 2.06 (s, 6H), 0.99 (t, *J* = 7.6 Hz, 3H).

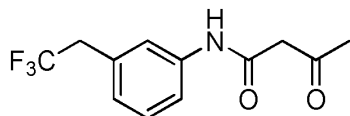
Synthesis of 194

[001032] **Step 1: Synthesis of 3-(2,2,2-trifluoroethyl)aniline (194-A)**



[001033] To suspension of (3-aminophenyl)boronic acid (300 mg, 2.19 mmol, 1.0 *eq*), 1,1,1-trifluoro-2-iodo-ethane (1.38 g, 6.57 mmol, 3.0 *eq*), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (253 mg, 438 μ mol, 0.2 *eq*) and cesium carbonate (1.43 g, 4.38 mmol, 2.0 *eq*) in dioxane (6 mL) and water (1 mL) was added tri(dibenzylideneacetone)dipalladium(0) (200 mg, 219 μ mol, 0.1 *eq*). The reaction was degassed and purged with nitrogen and then stirred at 80 °C for 12 h under nitrogen atmosphere. To the reaction mixture was added water (20 mL), and the suspension was
 20 extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 140 mg (36% yield) of **194-A** as a yellow solid.

[001034] **Step 2: Synthesis of 3-oxo-N-[3-(2,2,2-trifluoroethyl)phenyl]butanamide (194-B)**

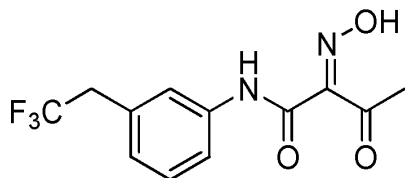


25

[001035] **194-B** was obtained *via* general procedure from **194-A**.

LCMS: (ESI) m/z : 260.1 $[M+H]^+$.

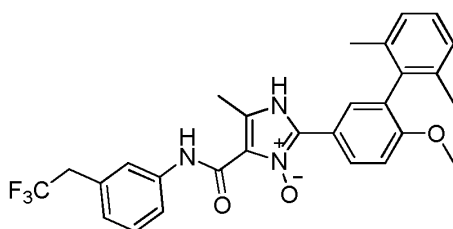
[001036] **Step 3: Synthesis of (*E*)-2-(hydroxyimino)-3-oxo-*N*-(3-(2,2,2-trifluoroethyl)phenyl)butanamide (194-C)**



5 [001037] **194-C** was obtained *via* general procedure from **194-B**.

[001038] LCMS: (ESI) m/z : 289.0 $[M+H]^+$.

[001039] **Step 4: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(2,2,2-trifluoroethyl)phenyl)carbamoyl)-1*H*-imidazole 3-oxide (194)**

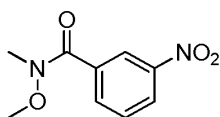


10 [001040] **194** was obtained *via* general procedure from **194-C** and **102-A**.

[001041] LCMS: (ESI) m/z : 510.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ : 13.55 (s, 1H), 13.15 (s, 1H), 8.53 (dd, J = 2.0, 8.8 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.75-7.65 (m, 2H), 7.37-7.31 (m, 2H), 7.20-7.11 (m, 3H), 7.07 (d, J = 7.6 Hz, 1H), 3.79 (s, 3H), 3.64 (d, J = 11.6 Hz, 2H), 2.58 (s, 3H), 1.96 (s, 6H).

15 **Synthesis of 195**

[001042] **Step 1: Synthesis of *N*-methoxy-*N*-methyl-3-nitrobenzamide (195-A)**

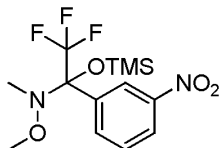


[001043] To a solution of 3-nitrobenzoic acid (5.00 g, 29.9 mmol, 1.0 *eq*) in *N,N*-dimethylformamide (50 mL) were added 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium (13.6 g, 35.9 mmol, 1.2 *eq*), triethylamine (9.08 g, 89.8 mmol, 3.0 *eq*) and *N*-methoxymethanamine (4.38 g, 44.9 mmol, 1.5 *eq*, hydrochloric acid). The mixture was stirred at 25 °C for 12 hr. The mixture was poured into saturated ammonium chloride (150 mL), then extracted with ethyl acetate (100 mL $\times$ 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/1) to give 4.50 g (72% yield) of **195-A**

as a yellow solid.

[001044] ¹H NMR (400 MHz, CDCl₃-d) δ: 8.58 (t, *J* = 1.6 Hz, 1H), 8.35-8.29 (m, 1H), 8.07-8.01 (m, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 3.56 (s, 3H), 3.41 (s, 3H).

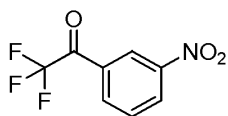
[001045] **Step 2: Synthesis of *N,O*-dimethyl-*N*-(2,2,2-trifluoro-1-(3-nitrophenyl)-1-((trimethylsilyl)oxy)ethyl)hydroxylamine (195-B)**



[001046] To a solution of **195-A** (1.00 g, 4.76 mmol, 1.0 *eq*) and cesium fluoride (145 mg, 951 μmol, 0.2 *eq*) in toluene (15 mL) was added trimethyl(trifluoromethyl)silane (1.35 g, 9.52 mmol, 2.0 *eq*) under 0 °C and stirred at 0 °C for 10 min. Then the mixture was warmed to 20 °C and stirred for 11 h
10 50 min. The mixture was poured into saturated sodium bicarbonate (50 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1.50 g (89% yield) of **195-B** as a yellow liquid.

[001047] ¹H NMR (400 MHz, CDCl₃-d) δ: 8.51 (s, 1H), 8.27-8.22 (m, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 3.61 (s, 3H), 2.33 (s, 3H), 0.33 (s, 9H).

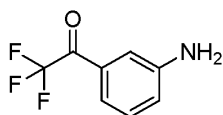
15 [001048] **Step 3: Synthesis of 2,2,2-trifluoro-1-(3-nitrophenyl)ethanone (195-C)**



[001049] To a solution of **195-B** (1.00 g, 2.84 mmol, 1.0 *eq*) in water (4 mL) was added tetrabutylammonium fluoride (1 M, 3 mL, 1.1 *eq*). The mixture was stirred at 50 °C for 2 h. The reaction was quenched by adding saturated sodium bicarbonate (60 mL). The aqueous phase was extracted with
20 ethyl acetate (25 mL × 2). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3/1) to give 420 mg (67% yield) of **195-C** as yellow liquid..

[001050] ¹H NMR (400 MHz, CDCl₃-d) δ: 8.92 (s, 1H), 8.61-8.57 (m, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 8.0 Hz, 1H).
25

[001051] **Step 4: Synthesis of 1-(3-aminophenyl)-2,2,2-trifluoroethanone (195-D)**

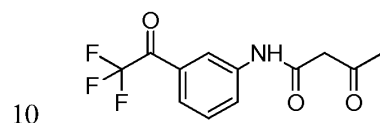


[001052] To a solution of **195-C** (170 mg, 776 μmol, 1.0 *eq*) in ethanol (5 mL) was added

stannous chloride (874 mg, 3.87 mmol, 5.0 *eq*). The mixture was stirred at 80 °C for 12 h. The reaction was quenched by adding saturated sodium bicarbonate (15 mL). The aqueous phase was extracted with ethyl acetate (10 mL x 2). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase HPLC (column: Phenomenex Synergi C18 150*25mm* 10um; mobile phase: [water (0.1% trifluoroacetic acid)-acetonitrile]; B%: 30%-60%, 10min) to give 80.0 mg (52% yield) of **195-D** as yellow gum.

[001053] **LCMS:** (ESI) *m/z*: 189.7 [M]⁺.

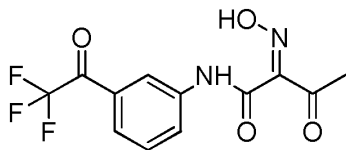
[001054] **Step 5: Synthesis of 3-oxo-N-(3-(2,2,2-trifluoroacetyl)phenyl)butanamide (195-E)**



[001055] **195-E** was obtained *via* general procedure from **195-D**.

[001056] **¹H NMR** (400 MHz, CDCl₃-*d*) δ: 9.50 (s, 1H), 8.21 (s, 1H), 8.03-7.99 (m, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.55-7.50 (m, 1H), 3.66 (s, 2H), 2.37 (s, 3H).

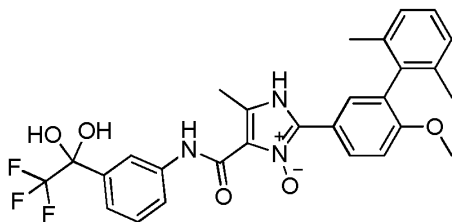
15 [001057] **Step 6: Synthesis of (Z)-2-(hydroxyimino)-3-oxo-N-(3-(2,2,2-trifluoroacetyl)phenyl)butanamide (195-F)**



[001058] **195-F** was obtained *via* general procedure from **195-E**.

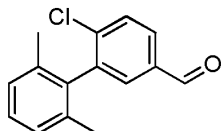
[001059] **LCMS:** (ESI) *m/z*: 303.0 [M+H]⁺.

20 [001060] **Step 7: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(2,2,2-trifluoro-1,1-dihydroxyethyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (195)**



[001061] **195** was obtained *via* general procedure from **195-F** and **102-A**.

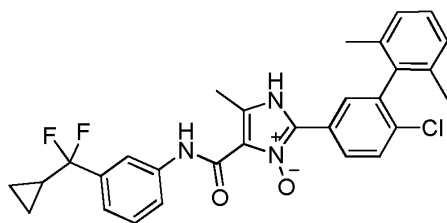
25 [001062] **LCMS:** *m/z* 542.0 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ: 8.40-8.37 (m, 1H), 7.97 (s, 1H), 7.90-7.86 (m, 1H), 7.81-7.76 (m, 1H), 7.50-7.42 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.17-7.13 (m, 1H), 7.11-7.07 (m, 2H), 3.84 (s, 3H), 2.65 (s, 3H), 2.01 (s, 6H).

Synthesis of 197**Step 1: Synthesis of 6-chloro-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (197-A)**

- 5 [001064] A mixture of 3-bromo-4-chloro-benzaldehyde (500 mg, 2.28 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (512 mg, 3.42 mmol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (658 mg, 569 μ mol, 0.25 *eq*), potassium phosphate (967 mg, 4.56 mmol, 2.0 *eq*) in 1,2-dimethoxyethane (10 mL) and water (2 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and
- 10 the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 160 mg (28% yield) of **197-A** as a yellow oil.

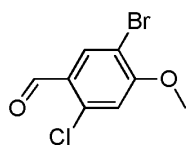
[001065] **LCMS:** (ESI) *m/z*: 244.9 [M+H]⁺.

- 15 [001066] **Step 2: Synthesis of 2-(6-chloro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (197)**



[001067] **197** was obtained *via* general procedure from **197-A** and **161-E**.

- [001068] **LCMS:** (ESI) *m/z*: 522.0 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.34 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.13 (d, *J* = 2.4 Hz, 1H), 7.98 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.25-7.20 (m, 1H), 7.17-7.13 (m, 2H), 2.68 (s, 3H), 2.03 (s, 6H), 1.67-1.53 (m, 1H), 0.73-0.68 (m, 4H)
- 20

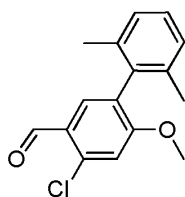
Synthesis of 198**Step 1: Synthesis of 5-bromo-2-chloro-4-methoxybenzaldehyde (198-A)**

25

[001070] To a solution of potassium bromide (1.74 g, 14.6 mmol, 5.0 *eq*) and bromine (936 mg, 5.86 mmol, 2.0 *eq*) in water (6mL) was added 2-chloro-4-methoxy-benzaldehyde (500 mg, 2.93 mmol, 1.0 *eq*) at 0 °C. The mixture was stirred at 20°C for 12 h. The suspension was filtrated and the filter cake was washed with water (30 mL). The filter cake was concentrated under reduced pressure to give a residue. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 160 mg (22% yield) of **198-A** as white solid.

[001071] ¹H NMR (400 MHz, CDCl₃-*d*) δ: 10.28 (s, 1H), 8.12 (s, 1H), 6.92 (s, 1H), 3.99 (s, 3H).

[001072] **Step 2: Synthesis of 4-chloro-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (198-B)**



10

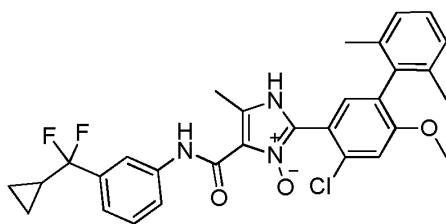
[001073] A mixture of **198-A** (50 mg, 196.40 umol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (29.5mg, 196 umol, 1.0 *eq*), potassium phosphate 62.5 mg, 294 umol, 1.5 *eq*), 2-dicyclohexylphosphino-2,6-dimethoxybiphenyl (40.3 mg, 98.2 umol, 0.5 *eq*) and tri(dibenzylideneaceton)dipalladium(0) (36.0, 39.3umol, 0.2 *eq*) in toluene (1 mL) and water (1 mL) was degassed and purged with nitrogen for 3 times. Then the mixture was stirred at 100 °C for 12 hr under nitrogen atmosphere. Then the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 20.0 mg (37% yield) of **198-B** as a white solid.

15

[001074] ¹H NMR (400 MHz, CDCl₃-*d*) δ: 10.45 (s, 1H), 7.73 (s, 1H), 7.25-7.23 (m, 1H), 7.17-7.16 (m, 2H), 7.08 (s, 1H), 3.90 (s, 3H), 2.04 (s, 6H).

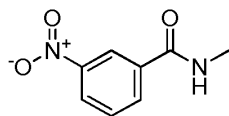
20

[001075] **Step 3: Synthesis of 2-(4-chloro-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (198)**



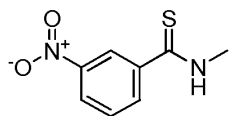
[001076] **198** was obtained *via* general procedure from **198-B** and **161-E**.

25 [001077] **LCMS:** *m/z*: 552.3 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ: 7.96 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.45-7.41 (m, 2H), 7.38 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.16-7.12 (m, 1H), 7.09-7.07 (m, 2H), 3.84 (s, 3H), 2.67 (s, 3H), 2.04 (s, 6H), 1.66-1.53 (m, 1H), 0.72-0.68 (m, 4H).

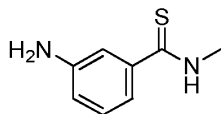
Synthesis of 196**Step 1: Synthesis of *N*-methyl-3-nitrobenzamide (196-A)**

[001079] To a solution of 3-nitrobenzoyl chloride (2.20 g, 11.8 mmol, 1.0 *eq*) in dichloromethane
 5 (30 mL) was added methanamine (960 mg, 14.2 mmol, 1.2 *eq*, hydrochloric acid) at 0 °C under nitrogen atmosphere. Then to the reaction was added dropwise triethylamine (3.60 g, 35.5 mmol, 3.0 *eq*) at 0 °C and the reaction mixture was stirred at 25 °C for 2 hr. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (30 mL),
 10 dried over anhydrous sodium sulfate, filtered and concentrated to give 1.66 g (crude) of **196-A** as a yellow oil.

[001080] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.83 (s, 1H), 8.67-8.64 (m, 1H), 8.40-8.35 (m, 1H), 8.29-8.25 (m, 1H), 7.80-7.75 (m, 1H), 2.82 (s, 3H)

Step 2: Synthesis of *N*-methyl-3-nitrobenzothioamide (196-B)

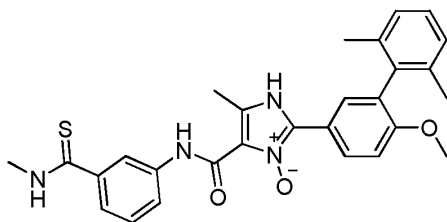
15 [001082] A suspension of **196-A** (830 mg, 4.61 mmol, 1.0 *eq*) and LAWESSON'S REAGENT (2.24 g, 5.53 mmol, 1.2 *eq*) in toluene (20 mL) was stirred at 110 °C for 4 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 900 mg (crude) of **196-B** as a brown oil.
 20

Step 3: Synthesis of 3-amino-*N*-methylbenzothioamide (196-C)

[001084] A suspension of **196-B** (300 mg, 1.53 mmol, 1.0 *eq*), iron powder (426 mg, 7.64 mmol, 5.0 *eq*) and ammonium chloride (408 mg, 7.64 mmol, 5.0 *eq*) in ethanol (20 mL) and water (2 mL) was
 25 stirred at 80 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum/ethyl acetate = 5/1) to give 160 mg (63% yield) of **196-C** as a yellow solid.

[001085] LCMS: (ESI) *m/z*: 167.0 [M+H]⁺.

Step 4: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-

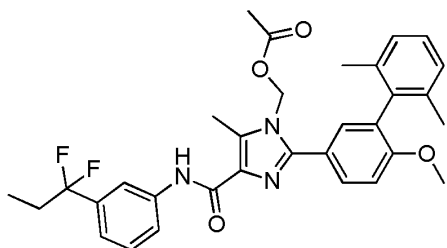
methyl-4-((3-(methylcarbamothioyl)phenyl)carbamoyl)-1*H*-imidazole 3-oxide (**196**)

[001087] To a solution of **196-C** (20 mg, 120 μ mol, 1.0 *eq*) in dichloromethane (2 mL) was added dropwise sodium bis(trimethylsilyl)amide (1 M, 144 μ L, 1.2 *eq*) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 0.5 hr. Then to the mixture was added a solution of **146-C** (54.9 mg, 144 μ mol, 1.2 *eq*) in dichloromethane (1 mL) at 0°C. The reaction was stirred at 40°C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Phenomenex Synergi C18 150*25mm* 10 μ m; mobile phase: [water(0.1%TFA)-ACN]; B%: 51%-81%,10min) to give 5 mg (6% yield) of **196** as a off-white solid.

10 [001088] **LCMS:** (ESI) *m/z*: 501.0 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.38 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.08 (t, *J* = 1.8 Hz, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.79-7.75 (m, 1H), 7.56-7.52 (m, 1H), 7.41-7.36 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.17-7.13 (m, 1H), 7.11-7.08 (m, 2H), 3.84 (s, 3H), 3.25 (s, 3H), 2.66 (s, 3H), 2.02 (s, 6H).

Synthesis of 200

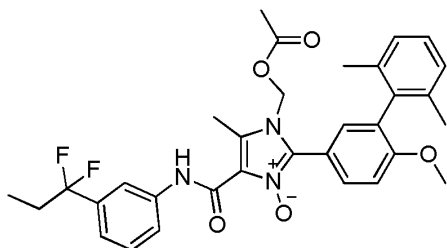
15 [001089] **Step 1: Synthesis of (4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazol-1-yl)methyl acetate (**200-A**)**



[001090] To a solution of **188-A** (100 mg, 204 μ mol, 1.0 *eq*) in *N,N*-dimethylformamide (2 mL) were added chloromethyl acetate (24.4 mg, 225 μ mol, 1.1 *eq*) and cesium carbonate (133 mg, 409 μ mol, 2.0 *eq*). The reaction mixture was stirred at 50 °C for 12 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 56%-86%, 8min) to give 70.0 mg (60% yield) of **200-A** as a white solid.

[001091] **LCMS:** (ESI) *m/z*: 562.4 [M+H]⁺.

25 [001092] **Step 2: Synthesis of 1-(acetoxymethyl)-4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-**

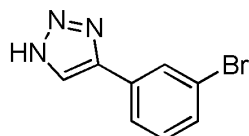
1H-imidazole 3-oxide (200)

[001093] To a solution of **200-A** (40.0 mg, 69.8 μmol , 1.0 *eq*) in dichloroethane (2 mL) was added 3-chlorobenzoperoxoic acid (15.1 mg, 69.8 μmol , 80% purity, 1.0 *eq*). The reaction mixture was stirred at 25 °C for 12 hr. The mixture was quenched with saturated sodium sulfite (10 mL) and then the mixture was extracted with dichloromethane (10 mL x 2). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3 μm ; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 50%-80%, 8min) to give 4.3 mg (10% yield) of **200** as a yellow solid.

[001094] **LCMS:** (ESI) m/z : 578.3 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 7.89 (s, 1H), 7.80 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.40-7.34 (m, 2H), 7.25 (d, $J = 7.2$ Hz, 1H), 7.17-7.12 (m, 1H), 7.10-7.07 (m, 2H), 5.95 (s, 2H), 3.86 (s, 3H), 2.83 (s, 3H), 2.22-2.14 (m, 2H), 2.03 (s, 6H), 2.02 (s, 3H), 0.98 (t, $J = 7.6$ Hz, 3H).

15 **Synthesis of 199**

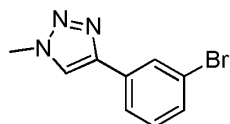
[001095] **Step 1: Synthesis of 4-(3-bromophenyl)-1H-1,2,3-triazole (199-A)**



[001096] A mixture of 1-bromo-3-ethynyl-benzene (500 mg, 2.76 mmol, 1.0 *eq*) and Copper iodide (26.3 mg, 138 μmol , 0.05 *eq*) in *N,N*-dimethylformamide (4.5mL) and methanol (0.5 mL) was degassed and purged with nitrogen for 3 times. Then trimethylsilyl azide (636 mg, 5.52 mmol, 2.0 *eq*) was added dropwise. The mixture was stirred at 100 °C for 12 hr under nitrogen atmosphere. To the mixture was added water (30 mL) and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 460 mg (74% yield) of **199-A** as a white solid.

[001097] **LCMS:** m/z 223.8 $[\text{M}+\text{H}]^+$.

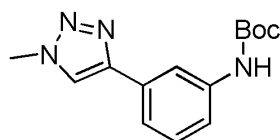
[001098] **Step 2: Synthesis of 4-(3-bromophenyl)-1-methyl-1H-1,2,3-triazole (199-B)**



[001099] To a solution of **199-A** (200 mg, 892 μmol , 1.0 *eq*) in *N,N*-dimethylformamide (2 mL) were added cesium carbonate (185 mg, 1.34 mmol, 1.5 *eq*) and iodomethane (190 mg, 1.34 mmol, 1.5 *eq*). The mixture was stirred at 20 °C for 2 hr. The mixture was quenched by addition of water (30 mL) slowly and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 200 mg (94% yield) mixture of **199-B** as a yellow oil.

[001100] **LCMS:** m/z : 238.1 $[\text{M}+\text{H}]^+$.

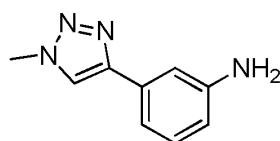
[001101] **Step 3: Synthesis of *tert*-butyl (3-(1-methyl-1*H*-1,2,3-triazol-4-yl)phenyl)carbamate (199-C)**



[001102] A mixture of **199-B** (200 mg, 840 μmol , 1.0 *eq*), *tert*-butyl carbamate (196 mg, 1.68 mmol, 2.0 *eq*), cesium carbonate (547 mg, 1.68 mmol, 2.0 *eq*), dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphane (80.1 mg, 168 μmol , 0.2 *eq*) and palladium acetate (18.8 mg, 84.0 μmol , 0.1 *eq*) in dioxane (3 mL) was degassed and purged with nitrogen for 3 times. The mixture was stirred at 90 °C for 12 hr under nitrogen atmosphere. The reaction mixture filtered and the filter liquor concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10/1) to give 80 mg (34% yield) of **199-C** as a yellow solid.

[001103] **LCMS:** (ESI) m/z : 275.1 $[\text{M}+\text{H}]^+$.

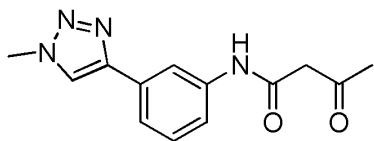
[001104] **Step 4: Synthesis of 3-(1-methyl-1*H*-1,2,3-triazol-4-yl)aniline (199-D)**



[001105] To a solution of *tert*-butyl **199-C** (80 mg, 291 μmol , 1.0 *eq*) in ethyl acetate (1 mL) was added hydrochloric acid/ethyl acetate (4 M, 1 mL). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to give 55 mg (89% yield, hydrochloride) of **199-D** as a yellow solid.

[001106] **LCMS:** (ESI) m/z : 175.0 $[\text{M}+\text{H}]^+$.

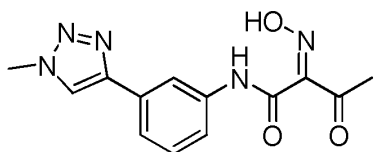
[001107] **Step 5: Synthesis of *N*-(3-(1-methyl-1*H*-1,2,3-triazol-4-yl)phenyl)-3-**

oxobutanamide (190-E)

[001108] **199-E** was obtained *via* general procedure from **199-D**.

[001109] **LCMS**: (ESI) *m/z*: 259.0 [M+H]⁺.

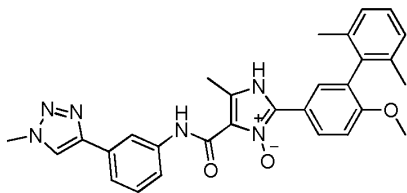
- 5 [001110] **Step 6: Synthesis of (Z)-2-(hydroxyimino)-N-(3-(1-methyl-1H-1,2,3-triazol-4-yl)phenyl)-3-oxobutanamide (199-F)**



[001111] **199-F** was obtained *via* general procedure from **199-E**.

[001112] **LCMS**: (ESI) *m/z*: 288.0 [M+H]⁺.

- 10 [001113] **Step 7: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(1-methyl-1H-1,2,3-triazol-4-yl)phenyl)carbamoyl)-1H-imidazole 3-oxide (199)**

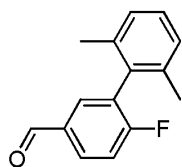


[001114] **199** was obtained *via* general procedure from **199-F** and **102-A**.

- [001115] **LCMS**: (ESI) *m/z*: 509.3 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ = 8.37 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.29 (s, 1H), 8.15 (t, *J* = 2.0 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.66-7.61 (m, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.17-7.13 (m, 1H), 7.10-7.08 (m, 2H), 4.16 (s, 3H), 3.83 (s, 3H), 2.65 (s, 3H), 2.02 (s, 6H).
- 15

Synthesis of 203

- [001116] **Step 1: Synthesis of 3-(2,6-dimethylphenyl)-4-fluoro-benzaldehyde (203-A)**

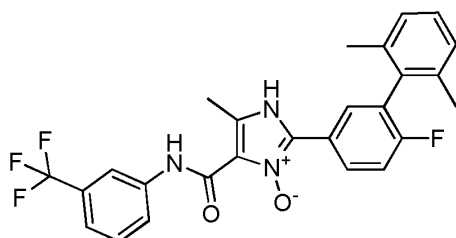


- 20 [001117] A mixture of 3-bromo-4-fluoro-benzaldehyde (100 mg, 493 μ mol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (111 mg, 739 μ mol, 1.5 *eq*), tetrakis(triphenylphosphine)palladium (114

mg, 98.5 μmol , 0.20 *eq*), potassium phosphate (209 mg, 985 μmol , 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (0.5 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 75 mg (67% yield) of **203-A** as off-white oil.

[001118] ¹H NMR (400 MHz, CDCl₃-d) δ : 10.0 (s, 1H), 7.94 (ddd, *J* = 2.0, 4.8, 8.4 Hz, 1H), 7.74 (dd, *J* = 2.0, 6.8 Hz, 1H), 7.34 (t, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 6.8 Hz, 1H), 7.18-7.12 (m, 2H), 2.06 (s, 6H).

- 10 [001119] **Step 2: Synthesis of 2-(6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(trifluoromethyl)phenyl)carbamoyl)-1*H*-imidazole 3-oxide (203)**

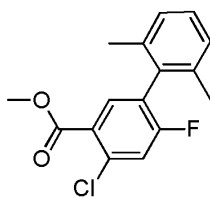


[001120] **203** was obtained *via* general procedure of **199-B** and **203-A**

- 15 [001121] **LCMS:** (ESI) *m/z*: 484.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 8.40-8.33 (m, 1H), 8.22 (s, 1H), 8.14 (dd, *J* = 2.4, 6.8 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.25-7.20 (m, 1H), 7.18-7.14 (m, 2H), 2.68 (s, 3H), 2.09 (s, 6H).

Synthesis of 204

- 20 [001122] **Step 1: Synthesis of methyl 4-chloro-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-carboxylate (204-A)**

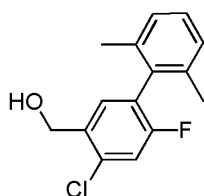


- 25 [001123] A mixture of methyl 5-bromo-4-chloro-2-fluoro-benzoate (100 mg, 374 μmol , 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (112 mg, 748 μmol , 1.5 *eq*), tetrakis[triphenylphosphine]palladium (85 mg, 75 μmol , 0.20 *eq*), potassium phosphate (159 mg, 748 μmol , 2.0 *eq*) in 1,2-dimethoxyethane (5 mL) and water (0.5 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous

sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/0) to give 20 mg (18% yield) of **204-A** as a yellow solid.

[001124] ¹H NMR (400 MHz, CDCl₃-d) δ: 7.78 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 10.4 Hz, 1H), 7.26-7.20 (m, 1H), 7.16-7.11 (m, 2H), 3.94-3.92 (m, 3H), 2.00 (s, 6H)

- 5 [001125] **Step 2: Synthesis of methyl (4-chloro-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol (204-B)**

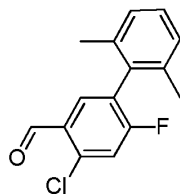


[001126] To a solution of **204-A** (20 mg, 68.3 umol, 1.0 *eq*) in tetrahydrofuran (1 mL) was added lithium tetrahydroborate (6.00 mg, 273 umol, 4.0 *eq*) at 0 °C. The mixture was stirred at 25 °C for 1 hr.

- 10 The reaction mixture was quenched by slow addition of saturated aqueous ammonium chloride (10 mL). Then the aqueous was extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 18 mg (crude) of **204-B** as a yellow solid.

- [001127] ¹H NMR (400 MHz, CDCl₃-d) δ: 7.34 (d, *J* = 2.4 Hz, 1H), 7.33-7.28 (m, 2H), 7.22-7.18 (m, 2H), 4.86 (s, 2H), 2.08 (s, 6H).

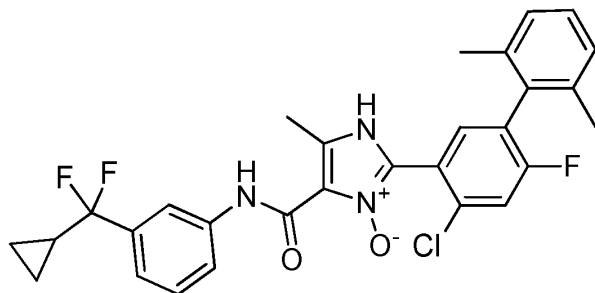
- [001128] **Step 3: Synthesis of methyl 4-chloro-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (204-C)**



- [001129] To a solution of **204-B** (9 mg, 34.0 umol, 1.0 *eq*) in dichloromethane (1 mL) was added Dess-Martin Periodinane (22 mg, 51.0 umol, 1.5 *eq*) at 25 °C. The reaction mixture was stirred at 25 °C for 0.5 hr. The mixture was quenched with saturated sodium bicarbonate solution (5 mL) and saturated sodium bisulfite (5 mL), and then extracted with ethyl acetate (5 mL x 2). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue to give 9 mg (crude) of **204-C** as a yellow solid.

- 25 [001130] ¹H NMR (400 MHz, CDCl₃-d) δ: 10.36 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 10.0 Hz, 1H), 7.26-7.21 (m, 1H), 7.14 (s, 1H), 7.13 (s, 1H), 1.98 (s, 6H).

- [001131] **Step 4: Synthesis of 2-(4-chloro-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide**

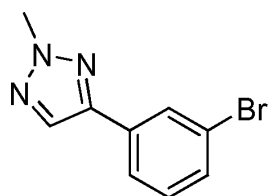


[001132] **204** was obtained via general procedure from **161-E** and **204-C**.

[001133] **LCMS:** (ESI) m/z : 540.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.28 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H), 7.67 (d, J = 10.4 Hz, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.25-7.20 (m, 1H), 7.17-7.13 (m, 2H), 2.70 (s, 3H), 2.05 (s, 6H), 1.64-1.54 (m, 1H), 0.72-0.67 (m, 4H).

Synthesis of 201

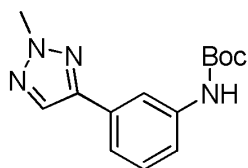
[001134] **Step 1: Synthesis of 4-(3-bromophenyl)-2-methyl-2H-1,2,3-triazole (201-A)**



[001135] To a solution of **199-A** (200 mg, 892 μ mol, 1.0 eq) in *N,N*-dimethylformamide (2 mL) were added cesium carbonate (185 mg, 1.34 mmol, 1.5 eq) and iodomethane (190 mg, 1.34 mmol, 1.5 eq). The mixture was stirred at 20 °C for 2 hr. The mixture was diluted by addition of water (30 mL) slowly and extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 200 mg (94% yield) mixture of **201-A** as a yellow oil.

[001136] **LCMS:** m/z : 238.1 $[M+H]^+$.

[001137] **Step 2: *tert*-butyl (3-(2-methyl-2H-1,2,3-triazol-4-yl)phenyl)carbamate (201-B)**

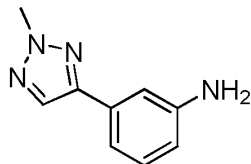


[001138] A mixture of **201-A** (200 mg, 840 μ mol, 1.0 eq), *tert*-butyl carbamate (196 mg, 1.68 mmol, 2.0 eq), cesium carbonate (547 mg, 1.68 mmol, 2.0 eq), dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphane (80.1 mg, 168 μ mol, 0.2 eq) and palladium acetate (18.8 mg, 84.0 μ mol, 0.1 eq) in dioxane (3 mL) was degassed and purged with nitrogen for 3 times. The mixture was stirred at 90 °C for 12 hr under nitrogen atmosphere. The reaction mixture filtered and the filtrate was

concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 170 mg (crude) of **201-B** as a yellow solid.

[001139] LCMS: (ESI) m/z : 275.1 $[M+H]^+$.

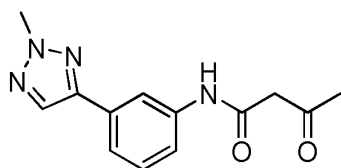
5 [001140] **Step 3: Synthesis of 3-(2-methyl-2H-1,2,3-triazol-4-yl)aniline (201-C)**



[001141] To a solution of **201-B** (170 mg, 291.63 μmol , 1.0 *eq*) in ethyl acetate (1mL) was added hydrochloric acid/ethyl acetate (4 M, 1 mL). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to give 130 mg (crude) of **201-C** as a yellow solid.

10 [001142] LCMS: (ESI) m/z : 175.0 $[M+H]^+$.

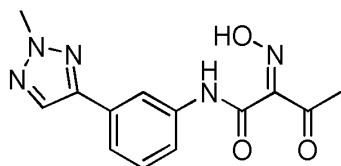
[001143] **Step 4: Synthesis of N-(3-(2-methyl-2H-1,2,3-triazol-4-yl)phenyl)-3-oxobutanamide (201-D)**



[001144] **201-D** was obtained *via* general procedure from **201-C**.

15 [001145] LCMS: (ESI) m/z : 259.0 $[M+H]^+$.

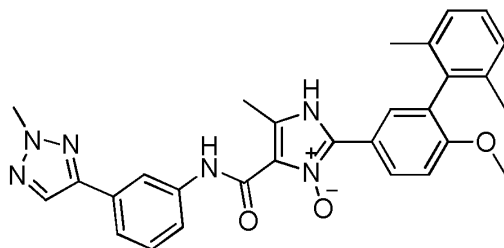
[001146] **Step 5: Synthesis of (Z)-2-(hydroxyimino)-N-(3-(2-methyl-2H-1,2,3-triazol-4-yl)phenyl)-3-oxobutanamide (201-E)**



[001147] **201-E** was obtained *via* general procedure from **201-D**.

20 [001148] LCMS: (ESI) m/z : 288.1 $[M+H]^+$.

[001149] **Step 6: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(2-methyl-2H-1,2,3-triazol-4-yl)phenyl)carbamoyl)-1H-imidazole 3-oxide (201)**

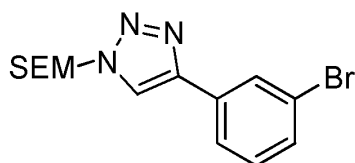


[001150] **201** was obtained *via* general procedure from **201-E** and **102-A**.

[001151] **LCMS:** (ESI) m/z : 509.3 $[M+H]^+$. **¹H NMR** (400 MHz, DMSO- d_6) δ : 13.64 (s, 1H), 8.54 (dd, J = 2.4, 8.8 Hz, 1H), 8.24 (s, 1H), 8.16-8.15 (m, 2H), 7.70-7.68 (m, 1H), 7.55-7.53 (m, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.20-7.16 (m, 1H), 7.14-7.12 (m, 2H), 4.21 (s, 3H), 3.79 (s, 3H), 2.59 (s, 3H), 1.97 (s, 6H).

Synthesis of 210

[001152] **Step 1: Synthesis of 4-(3-bromophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,3-triazole (210-A)**



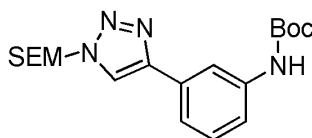
10

[001153] To a solution of **199-A** (1.0 g, 4.46 mmol, 1.0 *eq*) and *N,N*-diisopropylethylamine (1.2 g, 8.93 mmol, 2 *eq*) in *N,N*-dimethylformamide (10 mL) was added (2-(chloromethoxy)ethyl)trimethylsilane (1.1 g, 6.69 mmol, 1.5 *eq*) at 0 °C. The mixture was stirred at 20 °C for 12 hr. The mixture was quenched by slow addition of saturated aqueous ammonium chloride (30 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue 1.5 g (94% yield) mixture of **210-A** as a yellow oil.

15

[001154] **LCMS:** m/z : 356.1 $[M+H]^+$.

20 [001155] **Step 2: Synthesis of *tert*-butyl (3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,3-triazol-4-yl)phenyl)carbamate (210-B)**



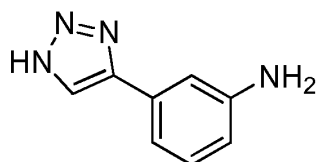
25

[001156] A mixture of **210-A** (1.5 g, 4.23 mmol, 1.0 *eq*), *tert*-butyl carbamate (991 mg, 8.47 mmol, 2.0 *eq*), cesium carbonate (2.0 g, 6.35 mmol, 2.0 *eq*), dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphane (403 mg, 846 μ mol, 0.2 *eq*) and palladium acetate (95 mg, 423 μ mol, 0.1

eq) in dioxane (20 mL) was degassed and purged with nitrogen for 3 times. The mixture was stirred at 90 °C for 12 hr under nitrogen atmosphere. The reaction mixture filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate=10/1) to give 1.0 g (crude) of **210-B** as a yellow solid.

5 [001157] **LCMS:** (ESI) *m/z*: 391.3 [M+H]⁺.

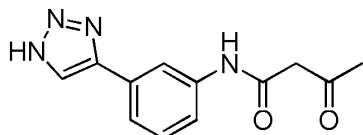
[001158] **Step 3: Synthesis of 3-(1*H*-1,2,3-triazol-4-yl)aniline (210-C)**



[001159] A mixture of **210-B** (1.0 g, 2.56 mmol, 1.0 *eq*) in trifluoroacetic acid (3 mL) and dichloromethane (9 mL) was stirred at 20 °C for 16 hr. The reaction mixture was poured into water (20
10 mL) and the mixture was extracted with ethyl acetate (2 × 30 mL). The pH of the aqueous phase was adjusted to around 7 by adding saturated sodium bicarbonate and the resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase HPLC (0.1% formic acid, water/acetonitrile from acetonitrile
15 0% to acetonitrile 15%) to give 100 mg (21% yield) of **210-C** as a yellow oil.

[001160] **LCMS:** (ESI) *m/z*: 161.1 [M+H]⁺.

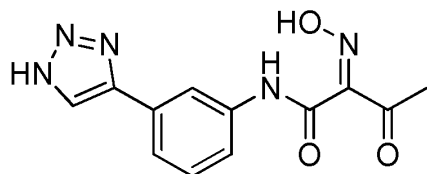
[001161] **Step 4: Synthesis of *N*-(3-(1*H*-1,2,3-triazol-4-yl)phenyl)-3-oxobutanamide (210-D)**



[001162] **210-D** was obtained *via* general procedure from **210-C**.

20 [001163] **LCMS:** (ESI) *m/z*: 245.1 [M+H]⁺.

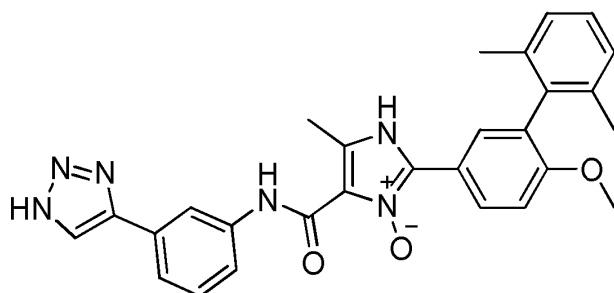
[001164] **Step 5: Synthesis of (Z)-*N*-(3-(1*H*-1,2,3-triazol-4-yl)phenyl)-2-(hydroxyimino)-3-oxobutanamide (210-E)**



[001165] **210-E** was obtained *via* general procedure from **210-D**.

25 [001166] **LCMS:** (ESI) *m/z*: 274.1 [M+H]⁺.

[001167] **Step 6: Synthesis of 4-((3-(1*H*-1,2,3-triazol-4-yl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1*H*-imidazole 3-oxide (210)**

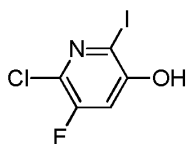


[001168] **210** was obtained *via* general procedure from **210-E** and **102-A**.

- 5 [001169] **LCMS:** (ESI) *m/z*: 495.3 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ : 15.16 (s, 1H), 13.63 (s, 1H), 8.55 (dd, *J* = 2.0, 8.8 Hz, 1H), 8.37 (s, 1H), 8.16 - 8.15 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.20 - 7.16 (m, 1H), 7.14 - 7.12 (m, 2H), 3.79 (s, 3H), 2.59 (s, 3H), 1.97 (s, 6H).

Synthesis of 202

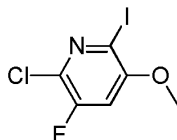
- 10 [001170] **Step 1: Synthesis of 6-chloro-5-fluoro-2-iodopyridin-3-ol (202-A)**



- [001171] To a solution of 6-chloro-5-fluoropyridin-3-ol (900 mg, 6.10 mmol, 1.0 *eq*) in water (20 mL) were added sodium carbonate (1.52 g, 18.3 mmol, 3.0 *eq*) and iodine (1.55 g, 6.10 mmol, 1.0 *eq*) in portions. The mixture was stirred at 25 °C for 1 hr. The mixture was adjusted to pH<5 by slow addition of hydrochloric acid (1M) and then solid precipitated. The resulting mixture was filtered and the filter cake was washed with water (20 mL) to give 1.60 g (crude) of **202-A** as a white solid.
- 15

[001172] **LCMS:** (ESI) *m/z*: 274.2[M+H]⁺.

[001173] **Step 2: Synthesis of 2-chloro-3-fluoro-6-iodo-5-methoxypyridine (202-B)**

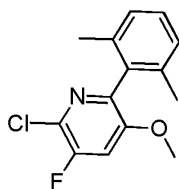


- 20 [001174] To a solution of **202-A** (1.60 g, 5.85 mmol, 1.0 *eq*) and potassium carbonate (1.21 g, 8.78 mmol, 1.5 *eq*) in acetone (20 mL) was added iodomethane (1.08 g, 7.61 mmol, 1.3 *eq*). The reaction mixture was stirred at 30 °C for 12 hr. The mixture was quenched with ammonium hydroxide (10 mL) and diluted with water (30 mL). Then the mixture was extracted with ethyl acetate (50 mL x 2). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and

concentrated under reduced pressure to give 1.60 g (crude) of **202-B** as a yellow solid.

[001175] ¹H NMR (400 MHz, CDCl₃-d) δ: 6.91 (d, *J* = 9.2 Hz, 1H), 3.93 (s, 3H).

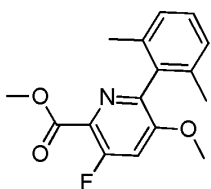
[001176] **Step 3: Synthesis of 2-chloro-6-(2,6-dimethylphenyl)-3-fluoro-5-methoxypyridine (202-C)**



5 [001177] A mixture of **202-B** (500 mg, 1.74 mmol, 1.0 *eq*), (2,6-dimethylphenyl)boronic acid (235 mg, 1.57 mmol, 0.9 *eq*), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (143 mg, 348 umol, 0.2 *eq*) and potassium phosphate (738 mg, 3.48 mmol, 2.0 *eq*), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (159 mg, 174 umol, 0.1 *eq*) in toluene (5 mL) and water (0.5 mL) was
10 degassed under vacuum and purged with nitrogen for 3 times. Then the mixture was stirred at 100 °C for 12 hr under nitrogen atmosphere. To the reaction mixture was added water (20 mL), and the suspension was extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl
15 acetate = 20/1) to give 400 mg (86% yield) of **202-C** as a yellow solid.

[001178] **LCMS:** (ESI) *m/z*: 266.3 [M+H]⁺.

[001179] **Step 4: Synthesis of methyl 6-(2,6-dimethylphenyl)-3-fluoro-5-methoxypicolinate (202-D)**

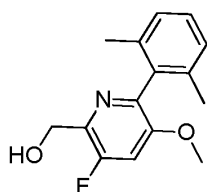


20 [001180] To a solution of **202-C** (100 mg, 376 umol, 1.0 *eq*) in methanol (2 mL) were added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (55.1 mg, 75.3 umol, 0.2 *eq*) and triethylamine (114 mg, 1.13 mmol, 3.0 *eq*). The reaction mixture was degassed under vacuum and purged with carbonic oxide several time, and then the mixture was stirred at 80 °C for 12 hr under carbonic oxide (50 Psi) atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue.
25 The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 30.0 mg (27% yield) of **202-D** as a white solid.

[001181] **LCMS:** (ESI) *m/z*: 290.3[M+H]⁺.

[001182] **Step 5: Synthesis of (6-(2,6-dimethylphenyl)-3-fluoro-5-methoxypyridin-2-**

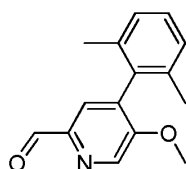
yl)methanol (202-E)



[001183] To a solution of **202-D** (30.0 mg, 104 μmol , 1.0 *eq*) in tetrahydrofuran (1 mL) was added lithium borohydride (9.04 mg, 415 μmol , 4.0 *eq*) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 2 hr under nitrogen atmosphere. The mixture was quenched with saturated ammonium chloride solution (5 mL) and then extracted with ethyl acetate (10 mL x 2). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 27.0 mg (crude) of **202-E** as a yellow oil.

[001184] **LCMS:** (ESI) m/z : 262.4[M+H]⁺.

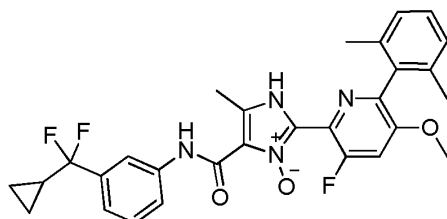
10 [001185] **Step 6: Synthesis of 6-(2,6-dimethylphenyl)-3-fluoro-5-methoxypicolinaldehyde (202-F)**



[001186] To a solution of **202-E** (27.0 mg, 103 μmol , 1.0 *eq*) in dichloroethane (1 mL) was added Dess-Martin periodinane (65.7 mg, 155 μmol , 1.5 *eq*). The reaction mixture was stirred at 25 °C for 1 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate= 5/1) to give 25.0 mg (93% yield) of **202-F** as a white solid.

[001187] **LCMS:** (ESI) m/z : 260.4[M+H]⁺.

20 [001188] **Step 7: Synthesis of 4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-2-(6-(2,6-dimethylphenyl)-3-fluoro-5-methoxypyridin-2-yl)-5-methyl-1H-imidazole 3-oxide (202)**



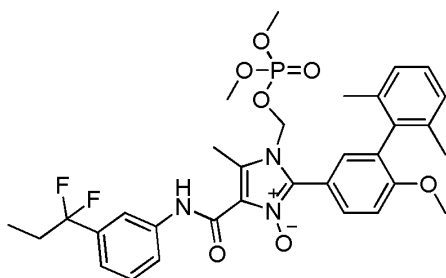
[001189] **202** was obtained *via* general procedure from **202-F** and **161-E**.

[001190] **LCMS:** (ESI) m/z : 537.3[M+H]⁺. ¹H NMR (400 MHz, MeOD-*d*₄) δ : 7.97 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 11.6 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.22-

7.16 (m, 1H), 7.14-7.06 (m, 2H), 3.91 (s, 3H), 2.65 (s, 3H), 2.02 (s, 6H), 1.67-1.54 (m, 1H), 0.74-0.67 (m, 4H).

Synthesis of 205

- [001191] **Step 1: Synthesis of 4-((3-(1,1-difluoropropyl)phenyl)carbamoyl)-1-
5 (((dimethoxyphosphoryl)oxy)methyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-
methyl-1H-imidazole 3-oxide (205)**

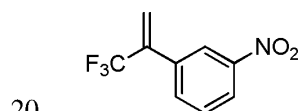


- [001192] To a solution of **193** (4.0 mg, 6.50 μmol , 1.0 *eq*) in methanol (0.5 mL) was added diazomethyl(trimethyl)silane (2 M, 32.5 μL , 10 *eq*). The reaction mixture was stirred at 25 °C for 12 hr.
10 The reaction was quenched by slow addition of acetic acid (0.5 mL) at 25 °C and the resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5 μm ; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 53%-83%, 10min) to give 2.0 mg (47% yield) of **205** as a yellow solid.

- [001193] **LCMS:** (ESI) m/z : 644.3 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 7.94-7.88 (m, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.47-7.38 (m, 3H), 7.26 (d, J = 7.6 Hz, 1H), 7.16-7.08 (m, 3H), 5.89 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.67 (d, J = 11.6 Hz, 6H), 2.86 (s, 3H), 2.21-2.13 (m, 2H), 2.05 (s, 6H), 0.98 (t, J = 7.6 Hz, 3H).
15

Synthesis of 206

- [001194] **Step 1: Synthesis of 1-nitro-3-(3,3,3-trifluoroprop-1-en-2-yl)benzene (206-A)**

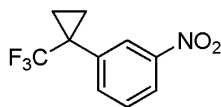


- [001195] A solution of **195-C** (100 mg, 456 μmol , 1.0 *eq*) in tetrahydrofuran (5 mL) was cooled to 0 °C under nitrogen atmosphere. To the reaction was added potassium tert-butoxide (102 mg, 913 μmol , 2.0 *eq*) in 3 portions and the reaction was stirred at 0 °C for 45 min. To the reaction mixture was added methyl(triphenyl)phosphonium;bromide (326 mg, 912 μmol , 2.0 *eq*) at 0 °C, then the reaction
25 was stirred under nitrogen atmosphere at 25 °C for 12 hr. The mixture was quenched by slow addition of saturated aqueous ammonium chloride (20 mL). The resulting mixture was transferred to a separatory funnel, and the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under

reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give a residue 25 mg (25% yield) mixture of **206-A** as a light yellow oil.

[001196] ¹H NMR (400 MHz, CDCl₃-d) δ: 8.34 (s, 1H), 8.29-8.26 (m, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 8.0Hz, 1H), 6.14 (d, *J* = 1.2 Hz, 1H), 5.93 (d, *J* = 1.2 Hz, 1H).

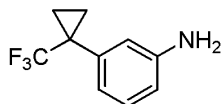
5 [001197] **Step 2: Synthesis of 1-nitro-3-(1-(trifluoromethyl)cyclopropyl)benzene (206-B)**



[001198] A solution of **206-A** (20 mg, 92.1 umol, 1.0 *eq*) and methyl(diphenyl)sulfonium;tetrafluoroborate (34 mg, 11 umol, 1.3 *eq*) in tetrahydrofuran (2 mL) was cooled to 0 °C. To the reaction mixture was added dropwise sodium bis(trimethylsilyl)amide (1 M, 147 uL, 1.6 *eq*) at 0 °C for 10 min, then reaction mixture was stirred at 25 °C for 1 hr. The mixture was quenched by slow addition of saturated aqueous ammonium chloride (5 mL). The resulting mixture was transferred to a separatory funnel, and the mixture was extracted with ethyl acetate (2 mL x 3). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20/1) to give 5.0 mg (23 yield) of **206-B** as a yellow oil.

[001199] ¹H NMR (400 MHz, CDCl₃-d) δ: 8.33 (s, 1H), 8.23-8.20 (m, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 8.0Hz, 1H), 1.49-1.46 (m, 2H), 1.11 (s, 2H).

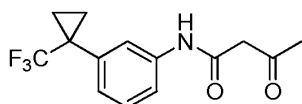
[001200] **Step 3: Synthesis of 3-(1-(trifluoromethyl)cyclopropyl)aniline (206-C)**



[001201] To a solution of **206-B** (5.0 mg, 21.6 umol, 1.0 *eq*) in methanol (1 mL) was added palladium 10% on carbon (1.0 mg, 10% purity). The suspension was degassed and purged with hydrogen several times. The reaction mixture was stirred under hydrogen (15 psi) atmosphere at 25 °C for 30 min. The suspension was filtered, and the filtrate was concentrated under reduced pressure to give 4.0 mg (crude) of **206-C** as a light yellow oil.

[001202] LCMS: (ESI) *m/z*: 202.1 [M+H]⁺.

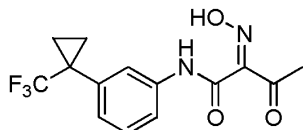
[001203] **Step 4: Synthesis of 3-oxo-N-(3-(1-(trifluoromethyl)cyclopropyl)phenyl)butanamide (206-D)**



30 [001204] **206-D** was obtained *via* general procedure from **206-C**.

[001205] LCMS: (ESI) m/z : 286.1 $[M+H]^+$.

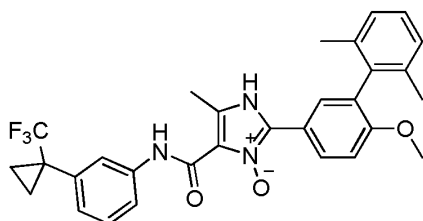
[001206] **Step 5: Synthesis of (Z)-2-(hydroxyimino)-3-oxo-N-(3-(1-(trifluoromethyl)cyclopropyl)phenyl)butanamide (206-E)**



5 [001207] **206-E** was obtained *via* general procedure from **206-D**.

[001208] LCMS: (ESI) m/z : 315.1 $[M+H]^+$.

[001209] **Step 6: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(1-(trifluoromethyl)cyclopropyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (206)**

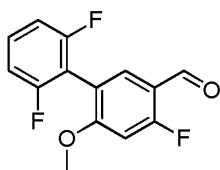


10 [001210] **206** was obtained *via* general procedure from **206-E** and **102-A**.

[001211] LCMS: (ESI) m/z : 536.4 $[M+H]^+$. ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ : 8.37 (dd, J = 2.4, 8.8 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.87 (s, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.16-7.12 (m, 1H), 7.10-7.08 (m, 2H), 3.83 (s, 3H), 2.64 (s, 3H), 2.02 (s, 6H), 1.38-1.35 (m, 2H), 1.13-1.12 (m, 2H).

15 **Synthesis of 207**

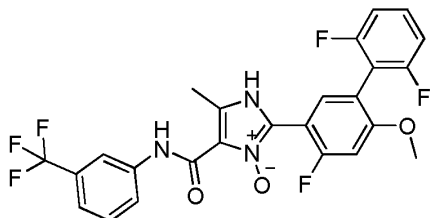
[001212] **Step 1: Synthesis of 2',4,6'-trifluoro-6-methoxy-[1,1'-biphenyl]-3-carbaldehyde (207-A)**



20 [001213] A mixture of **125-A** (141 mg, 607 μmol , 1.2 *eq*), (2,6-difluorophenyl)boronic acid (80.0 mg, 506 μmol , 1.0 *eq*), tri(dibenzylideneacetone)dipalladium(0) (46.3 mg, 50.6 μmol , 0.1 *eq*), dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl]phosphane (41.6 mg, 101 μmol , 0.2 *eq*) and potassium phosphate (215 mg, 1.01 mmol, 2.0 *eq*) in toluene (2 mL) and water (0.2 mL) was stirred at 100 °C for 12 hr under nitrogen atmosphere. The mixture was poured into saturated ammonium chloride (10 mL), extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layer was washed with brine (10 mL),

dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (silica gel, Petroleum ether/Ethyl acetate from 1/0 to 30/1) to give 100 mg (74% yield) of **207-A** as a yellow solid.

[001214] **Step 2: Synthesis of 5-methyl-2-(2',4,6'-trifluoro-6-methoxy-[1,1'-biphenyl]-3-yl)-4-((3-(trifluoromethyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (207)**

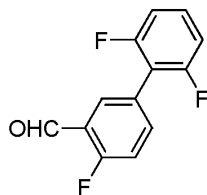


[001215] **207** was obtained *via* general procedure from **207-A** and **171-B**.

[001216] **LCMS:** (ESI) *m/z*: 522.0 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-*d*₆) δ : 8.17 (s, 1H), 8.05 (s, 1H), 7.67-7.61 (m, 1H), 7.53-7.43 (m, 2H), 7.38-7.31 (m, 1H), 7.17-7.09 (m, 3H), 3.76 (s, 3H), 2.42 (s, 3H).

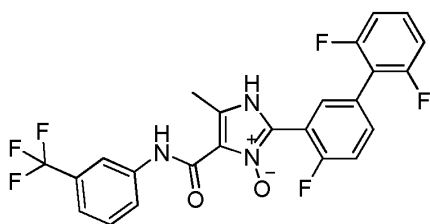
Synthesis of 212

[001217] **Step 1: Synthesis of 2',4,6'-trifluoro-[1,1'-biphenyl]-3-carbaldehyde (212-A)**



[001218] A mixture of 5-bromo-2-fluoro-benzaldehyde (123 mg, 607 μ mol, 1.2 *eq*), (2,6-difluorophenyl)boronic acid (80.0 mg, 506 μ mol, 1.0 *eq*), tri(dibenzylideneacetone)dipalladium(0) (46.3 mg, 50.6 μ mol, 0.1 *eq*), dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl]phosphane (41.6 mg, 101 μ mol, 0.2 *eq*) and potassium phosphate (215 mg, 1.01 mmol, 2.0 *eq*) in toluene (2 mL) and water (0.2 mL) was stirred at 100 °C for 12 hr under nitrogen atmosphere. The mixture was poured into saturated ammonium chloride (10 mL), extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (silica gel, Petroleum ether/Ethyl acetate from 1/0 to 30/1) to give 100 mg (83% yield) of **212-A** as a yellow solid.

[001219] **Step 2: Synthesis of 5-methyl-2-(2',4,6'-trifluoro-[1,1'-biphenyl]-3-yl)-4-((3-(trifluoromethyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (212)**

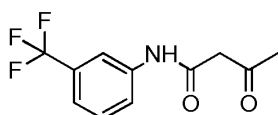


[001220] **212** was obtained *via* general procedure from **212-A** and **171-B**.

[001221] **LCMS:** (ESI) m/z : 492.2 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 8.50 (d, J = 6.0 Hz, 1H), 8.22 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.74-7.69 (m, 1H), 7.56-7.50 (m, 2H), 7.49-7.40 (m, 2H), 7.17-7.09 (m, 2H), 2.71 (s, 3H).

Synthesis of 171

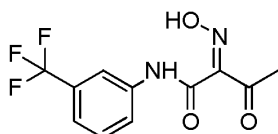
[001222] **Step 1: Synthesis of 3-oxo-N-(3-(trifluoromethyl)phenyl)butanamide (171-A)**



[001223] **171-A** was obtained *via* general procedure from 3-(trifluoromethyl)aniline.

10 [001224] **LCMS:** (ESI) m/z : 246.1 $[M+H]^+$.

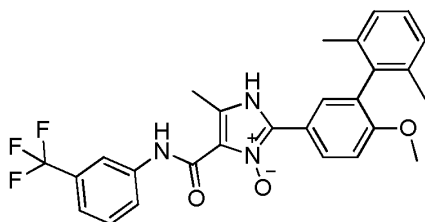
[001225] **Step 2: Synthesis of (Z)-2-(hydroxyimino)-3-oxo-N-(3-(trifluoromethyl)phenyl)butanamide (171-B)**



[001226] **171-B** was obtained *via* general procedure from **171-A**.

15 [001227] **LCMS:** (ESI) m/z : 275.0 $[M+H]^+$.

[001228] **Step 3: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(trifluoromethyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (171)**



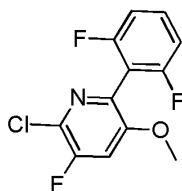
[001229] **171** was obtained *via* general procedure from **171-B** and **102-A**.

20 [001230] **LCMS:** (ESI) m/z : 496.3 $[M+H]^+$. **¹H NMR** (400 MHz, MeOD- d_4) δ : 8.38-8.34 (m, 1H), 8.22 (s, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.42 (d, J

= 8.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.16-7.08 (m, 3H), 3.84 (s, 3H), 2.66 (s, 3H), 2.02 (s, 6H).

Synthesis of 208

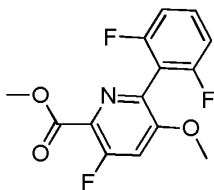
[001231] **Step 1: Synthesis of 2-chloro-6-(2,6-difluorophenyl)-3-fluoro-5-methoxypyridine (208-A)**



5 [001232] To a solution of **202-B** (300 mg, 1.04 mmol, 1.0 *eq*), (2,6-difluorophenyl)boronic acid (148 mg, 939 μ mol, 0.9 *eq*), 1,10-phenanthroline (18.8 mg, 104 μ mol, 0.1 *eq*) and cesium fluoride (317 mg, 2.09 mmol, 2.0 *eq*) in *N,N*-dimethylformamide (3 mL) was added copper iodide (19.9 mg, 104 μ mol, 0.1 *eq*). The mixture was degassed under vacuum and purged with nitrogen several time then
10 stirred at 130 °C for 12 hr. To the reaction mixture was added water (10 mL), and the suspension was extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 70.0 mg (24% yield) of **208-A** as a yellow solid.

15 [001233] **LCMS:** (ESI) m/z : 274.2 $[M+H]^+$.

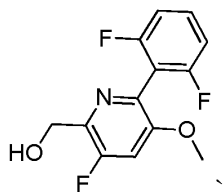
[001234] **Step 2: Synthesis of methyl 6-(2,6-difluorophenyl)-3-fluoro-5-methoxypyridine-2-carboxylate (208-B)**



[001235] To a solution of **208-A** (70.0 mg, 256 μ mol, 1.0 *eq*) in methanol (2 mL) were added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (37.4 mg, 51.2 μ mol, 0.2 *eq*) and triethylamine (77.7 mg, 767 μ mol, 3.0 *eq*). The reaction mixture was degassed under vacuum and purged with carbonic
20 oxide several time, and then the mixture was stirred at 80 °C for 12 hr under carbonic oxide (50 Psi) atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give
25 40.0 mg (52% yield) of **208-B** as a white solid.

[001236] **LCMS:** (ESI) m/z : 298.3 $[M+H]^+$.

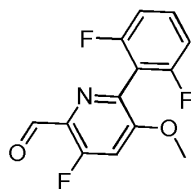
[001237] **Step 3: Synthesis of (6-(2,6-difluorophenyl)-3-fluoro-5-methoxypyridin-2-yl)methanol (208-C)**



[001238] To a solution of **208-B** (40.0 mg, 135 μmol , 1.0 *eq*) in tetrahydrofuran (4 mL) was added lithium borohydride (11.7 mg, 538 μmol , 4.0 *eq*) at 0 °C under nitrogen atmosphere. Then the mixture was warmed to 25 °C and stirred for another 2 hr. The mixture was quenched by saturated ammonium chloride solution (10 mL) and then extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 35.0 mg (crude) of **208-C** as a yellow oil.

[001239] **LCMS:** (ESI) m/z : 270.3[M+H]⁺.

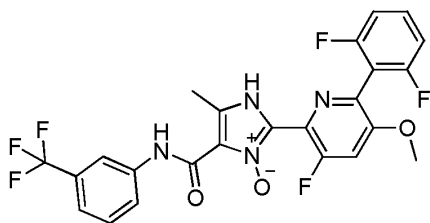
[001240] **Step 4: Synthesis of 6-(2,6-difluorophenyl)-3-fluoro-5-methoxypicolinaldehyde (208-D)**



[001241] To a solution of **208-C** (35.0 mg, 130 μmol , 1.0 *eq*) in dichloroethane (2 mL) was added Dess-Martin periodinane (82.7 mg, 195 μmol , 1.5 *eq*). The mixture was stirred at 25 °C for 3 hr. The mixture was quenched with saturated sodium thiosulfate (10 mL) and sodium bicarbonate (10 mL), and then the mixture was extracted with dichloromethane (20 mL x 2). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate= 5/1) to give 10.0 mg (28% yield) of **208-D** as a yellow solid.

[001242] **LCMS:** (ESI) m/z : 268.3 [M+H]⁺.

[001243] **Step 5: Synthesis of 2-(6-(2,6-difluorophenyl)-3-fluoro-5-methoxypyridin-2-yl)-5-methyl-4-((3-(trifluoromethyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (208)**



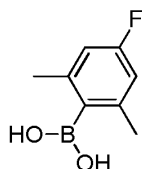
[001244] **208** was obtained *via* general procedure from **208-D** and **199-B**.

[001245] **LCMS:** (ESI) m/z : 523.2 [M+H]⁺. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 8.20 (s, 1H), 7.80

(d, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 11.2$ Hz, 1H), 7.57-7.46 (m, 2H), 7.42 (d, $J = 7.6$ Hz, 1H), 7.07 (t, $J = 7.6$ Hz, 2H), 3.97 (s, 3H), 2.66 (s, 3H).

Synthesis of 209

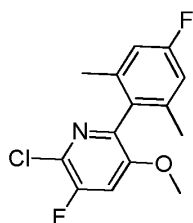
[001246] Step 1: Synthesis of (4-fluoro-2,6-dimethylphenyl)boronic acid (209-A)



[001247] To a solution of 2-bromo-5-fluoro-1,3-dimethyl-benzene (2.00 g, 9.85 mmol, 1.0 *eq*) in THF (20 mL) was added slowly butyllithium (2.5 M, 4.33 mL, 1.1 *eq*) at -78 °C via syringe under nitrogen atmosphere. After stirred at -78 °C for 45 min, trimethyl borate (1.23 g, 11.8 mmol, 1.2 *eq*) was added dropwise to the mixture at -78 °C. The mixture was stirred at -78 °C for 15 min and then warmed to 25 °C for another 1 hr. The mixture was quenched with hydrogen chloride (1M, 30 mL) at 25 °C and stirred for another 2 hr. The resulting mixture was extracted with ethyl acetate (50 mL x 2). The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was triturated with petroleum ether (10 mL) to give 400 mg (24% yield) of **209-A** as a white solid.

[001248] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.16 (s, 2H), 6.75 (d, $J = 10.4$ Hz, 2H), 2.27 (s, 6H).

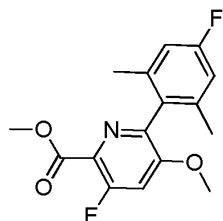
[001249] Step 2: Synthesis of 2-chloro-3-fluoro-6-(4-fluoro-2,6-dimethylphenyl)-5-methoxypyridine (209-B)



[001250] To a solution of **209-A** (158 mg, 939 μmol , 0.9 *eq*), **202-B** (300 mg, 1.04 mmol, 1.0 *eq*), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (85.7 mg, 209 μmol , 0.2 *eq*) and potassium phosphate (443 mg, 2.09 mmol, 2.0 *eq*) in toluene (3 mL) and water (0.3 mL) was added tri(dibenzylideneacetone)dipalladium(0) (95.6 mg, 104 μmol , 0.1 *eq*). The mixture was degassed under vacuum and purged with nitrogen several time, then stirred at 100 °C for 12 hr. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (30 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to give 180 mg (crude) of **209-B** as a yellow oil.

[001251] LCMS: (ESI) m/z : 284.3 $[M+H]^+$.

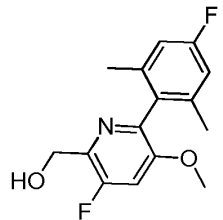
[001252] **Step 3: Synthesis of methyl 3-fluoro-6-(4-fluoro-2,6-dimethylphenyl)-5-methoxypicolinate (209-C)**



- 5 [001253] To a solution of **209-B** (180 mg, 634 μmol , 1.0 eq) in methanol (2 mL) were added 1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (92.9 mg, 127 μmol , 0.2 eq) and triethylamine (193 mg, 1.90 mmol, 3.0 eq). The reaction mixture was degassed under vacuum and purged with carbonic oxide several time, and then the mixture was stirred at 80 °C for 12 hr under carbonic oxide (50 Psi) atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue.
- 10 The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 100 mg (50% yield) of **209-C** as a white solid.

[001254] LCMS: (ESI) m/z : 308.3 $[M+H]^+$.

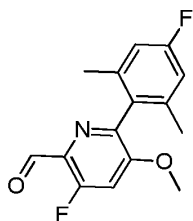
[001255] **Step 4: Synthesis of (3-fluoro-6-(4-fluoro-2,6-dimethylphenyl)-5-methoxypyridin-2-yl)methanol (209-D)**



- 15 [001256] To a solution of **209-C** (100 mg, 322 μmol , 1.0 eq) in tetrahydrofuran (2 mL) was added lithium borohydride (28.1 mg, 1.29 mmol, 4.0 eq) at 0 °C under nitrogen atmosphere. Then the mixture was warmed to 25 °C and stirred for another 1 hr. The mixture was quenched by saturated ammonium chloride solution (20 mL) and then extracted with ethyl acetate (20 mL x 2). The combined organic layer
- 20 was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 90.0 mg (crude) of **209-D** as a white solid.

[001257] LCMS: (ESI) m/z : 280.3 $[M+H]^+$.

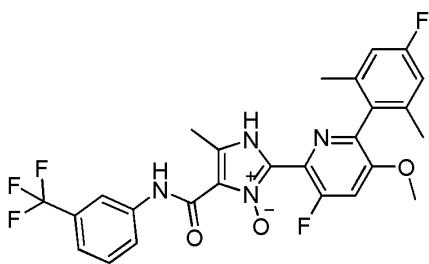
[001258] **Step 5: Synthesis of 3-fluoro-6-(4-fluoro-2,6-dimethylphenyl)-5-methoxypicolinaldehyde (209-E)**



[001259] To a solution of **209-D** (90.0 mg, 322 μmol , 1.0 *eq*) in dichloroethane (2 mL) was added dess-martin periodinane (273 mg, 645 μmol , 2.0 *eq*). The mixture was stirred at 25 °C for 2 hr. The mixture was quenched with saturated sodium thiosulfate (5 mL) and sodium bicarbonate (5 mL), and then the mixture was extracted with dichloromethane (10 mL x 2). The organic layer was combined and washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (petroleum ether/ethyl acetate= 5/1) to give 15.0 mg (16% yield) of **209-E** as a white solid.

[001260] **LCMS:** (ESI) m/z : 278.3 $[\text{M}+\text{H}]^+$.

10 [001261] **Step 6: Synthesis of 2-(3-fluoro-6-(4-fluoro-2,6-dimethylphenyl)-5-methoxypyridin-2-yl)-5-methyl-4-((3-(trifluoromethyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (209)**

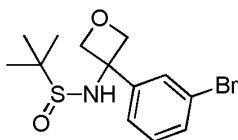


[001262] **209** was obtained *via* general procedure from **209-E** and **199-B**.

15 [001263] **LCMS:** (ESI) m/z : 533.2 $[\text{M}+\text{H}]^+$. **^1H NMR** (400 MHz, $\text{MeOD}-d_4$) δ : 8.21 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 11.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 6.86 (d, J = 9.6 Hz, 2H), 3.93 (s, 3H), 2.67 (s, 3H), 2.02 (s, 6H).

Synthesis of 211

20 [001264] **Step 1: Synthesis of N-(3-(3-bromophenyl)oxetan-3-yl)-2-methylpropane-2-sulfonamide (211-A)**



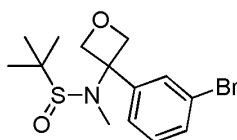
[001265] A solution of 1,3-dibromobenzene (6.06 g, 25.6 mmol, 1.5 *eq*) in tetrahydrofuran (60 mL) was degassed and purged with nitrogen, then chilled to -78 °C. To the solution was dropwise added

n-butyllithium (2.5 M, 8.22 mL, 1.2 *eq*) at -78 °C. After completion of addition, the solution was stirred at -78 °C for 1 h. Then to the reaction was added dropwise a solution of 2-methyl-*N*-(oxetan-3-ylidene)propane-2-sulfonamide (3.00 g, 17.1 mmol, 1.0 *eq*) in THF (6 mL) at -78 °C. After completion of addition, the reaction mixture was stirred at -78 °C under nitrogen atmosphere for an additional 1 hr.

The reaction was quenched by slow addition of saturated aqueous ammonium chloride (50 mL), and the suspension was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 5.69 g (crude) of **211-A** as a yellow oil.

[001266] LCMS: (ESI) *m/z*: 332.1 [M+H]⁺

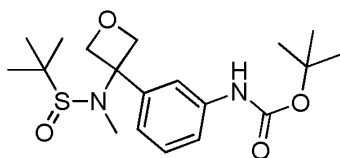
10 [001267] **Step 2: Synthesis of *N*-(3-(3-bromophenyl)oxetan-3-yl)-*N*,2-dimethylpropane-2-sulfonamide (211-B)**



[001268] To a solution of **211-A** (5.69 g, 17.1 mmol, 1.0 *eq*) in THF (60 mL) was added sodium hydride (753 mg, 18.8 mmol, 60% purity, 1.1 *eq*) at 0 °C under nitrogen atmosphere for 30 min. Then iodomethane (3.65 g, 25.6 mmol, 1.5 *eq*) was added into the reaction mixture at 0 °C. The mixture was stirred at 25 °C for 2 h under nitrogen atmosphere. The reaction was quenched by slow addition of saturated aqueous ammonium chloride (50 mL), and the suspension was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silica gel, Petroleum ether/Ethyl acetate from 1/0 to 3/1) to give 4.00 g (64% yield) of **211-B** as a yellow oil.

[001269] LCMS: (ESI) *m/z*: 348.1 [M+H]⁺.

[001270] **Step 3: Synthesis of *tert*-butyl (3-(3-(*N*,2-dimethylpropan-2-ylsulfonamido)oxetan-3-yl)phenyl)carbamate (211-C)**



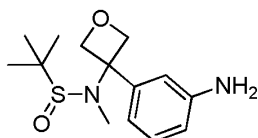
25 [001271] A suspension of **211-B** (1.00 g, 2.76 mmol, 1.0 *eq*), *tert*-butyl carbamate (635 mg, 4.14 mmol, 1.5 *eq*), palladium acetate (61.9 mg, 275. μmol, 0.1 *eq*), dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphane (262 mg, 551 μmol, 0.2 *eq*), cesium carbonate (2.70 g, 8.27 mmol, 3.0 *eq*) in dioxane (20 mL) was stirred at 90 °C for 12 h under nitrogen atmosphere. The mixture was filtered, and the filtrate was diluted with water (40 mL). The resulting suspension was extracted with ethyl acetate

30

(30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/1) to give 1.6 g (50% yield) of **211-C** as a yellow solid.

5 [001272] LCMS: (ESI) m/z : 383.1 $[M+H]^+$

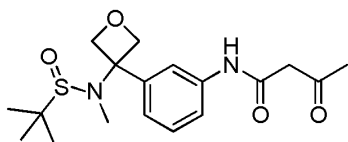
[001273] **Step 4: Synthesis of *N*-(3-(3-aminophenyl)oxetan-3-yl)-*N*,2-dimethylpropan-2-sulfinamide (211-D)**



[001274] To a solution of **211-C** (600 mg, 1.54 mmol, 1.0 *eq*) in dry dichloromethane (12 mL)
10 were added TMSOTf (1.37 g, 6.17 mmol, 4.0 *eq*) and 2,6-LUTIDINE (826 mg, 7.71 mmol, 5.0 *eq*) at -40 °C. Then the reaction mixture was stirred for 2 hr at -40 °C. The reaction was quenched by slowly addition of saturated sodium carbonate (20 mL) at 0 °C and the resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was
15 purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1/3) to give 100 mg (18% yield) of **211-D** as a yellow solid.

[001275] LCMS: (ESI) m/z : 283.1 $[M+H]^+$.

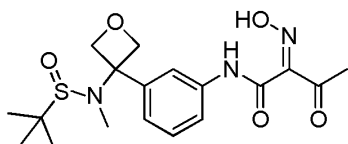
[001276] **Step 5: Synthesis of *N*-(3-(3-(*N*,2-dimethylpropan-2-ylsulfinamido)oxetan-3-yl)phenyl)-3-oxobutanamide (211-E)**



20 [001277] **211-E** was obtained *via* general procedure from **211-D**.

[001278] LCMS: (ESI) m/z : 367.3 $[M+H]^+$.

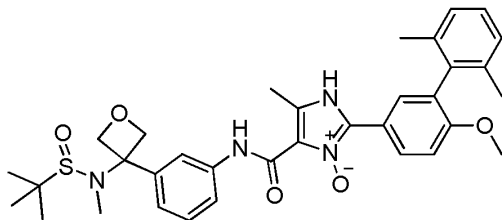
[001279] **Step 6: Synthesis of (Z)-*N*-(3-(3-(*N*,2-dimethylpropan-2-ylsulfinamido)oxetan-3-yl)phenyl)-2-(hydroxyimino)-3-oxobutanamide (211-F)**



25 [001280] **211-F** was obtained *via* general procedure from **211-E**.

[001281] LCMS: (ESI) m/z : 396.1 $[M+H]^+$.

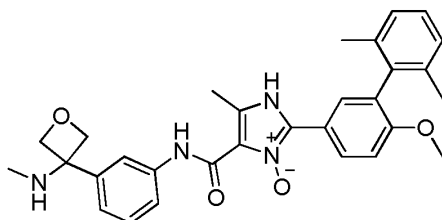
[001282] **Step 7: Synthesis of 4-((3-(3-(N,2-dimethylpropan-2-ylsulfonamido)oxetan-3-yl)phenyl)carbamoyl)-2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-1H-imidazole 3-oxide (211-G)**



5 [001283] **211-G** was obtained *via* general procedure from **211-F** and **102-A**.

[001284] **LCMS:** (ESI) m/z : 617.2 $[M+H]^+$.

[001285] **Step 8: Synthesis of 2-(6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(3-(methylamino)oxetan-3-yl)phenyl)carbamoyl)-1H-imidazole 3-oxide (211)**



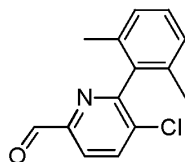
10

[001286] A solution of **211-G** (30.0 mg, 72.1 μ mol, 1.0 *eq*) in hydrogen chloride in ethyl acetate (4 M, 3 mL) was stirred at 25 °C for 30 min. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Phenomenex luna C18 150*25mm* 10 μ m; mobile phase: [water(0.2%FA)-ACN]; B%: 20%-40%,10min) to give 10 mg (79%
15 yield) of **211** as a white solid

[001287] **LCMS:** (ESI) m/z : 513.4 $[M+H]^+$. **¹H NMR** (400 MHz, DMSO- d_6) δ : 13.98-13.90 (m, 1H), 8.50-8.40 (m, 1H), 8.29-8.26 (m, 2H), 7.69-7.63 (m, 1H), 7.61-7.56 (m, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.19 (s, 2H), 7.12-7.08 (m, 2H), 7.04-6.99 (m, 1H), 4.74-4.69 (m, 2H), 4.65-4.61 (m, 2H), 3.74 (s, 3H), 2.44 (s, 3H), 2.03 (s, 3H), 1.96 (s, 6H).

20 **Synthesis of 213**

[001288] **Step 1: Synthesis of 5-chloro-6-(2,6-dimethylphenyl)picolinaldehyde (213-A)**

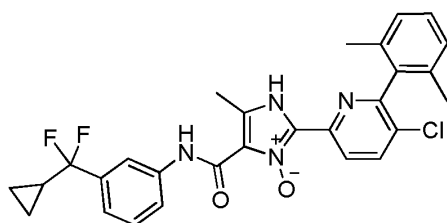


[001289] To a solution of (2,6-dimethylphenyl)boronic acid (51.0 mg, 340 μ mol, 1.5 *eq*), 6-

bromo-5-chloro-pyridine-2-carbaldehyde (50.0 mg, 227 μmol , 1.0 *eq*), potassium phosphate (96.3 mg, 454 μmol , 2.0 *eq*) and (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (9.31 mg, 22.7 μmol , 0.1 *eq*) in water (0.2 mL) and toluene (1 mL) was added tri(dibenzylideneacetone)dipalladium(0) (20.8 mg, 22.7 μmol , 0.1 *eq*). The mixture was degassed under vacuum and purged with nitrogen several times, then stirred at 100 °C for 4 h. The reaction was diluted with water (20 mL) and the resulting mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give 30 mg (54% yield) of **213-A** as a yellow oil.

[001290] **LCMS:** (ESI) m/z : 246.1 $[\text{M}+\text{H}]^+$.

[001291] **Step 2: 2-(5-chloro-6-(2,6-dimethylphenyl)pyridin-2-yl)-4-((3-(cyclopropyldifluoromethyl)phenyl)carbamoyl)-5-methyl-1H-imidazole 3-oxide (213)**

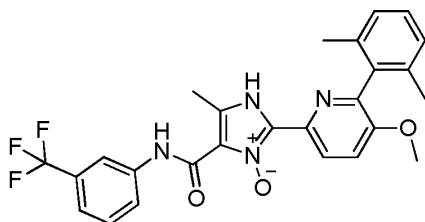


[001292] **213** was obtained via general procedure from **161-E** and **213-A**.

[001293] **LCMS:** (ESI) m/z : 523.1 $[\text{M}+\text{H}]^+$. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 9.05 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.98 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.27-7.22 (m, 1H), 7.17-7.12 (m, 2H), 2.62 (s, 3H), 2.03 (s, 6H), 1.67-1.57 (m, 1H), 0.76-0.69 (m, 4H).

Synthesis of 214

[001294] **Step 1: 2-(6-(2,6-dimethylphenyl)-5-methoxypyridin-2-yl)-5-methyl-4-((3-(trifluoromethyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (214)**



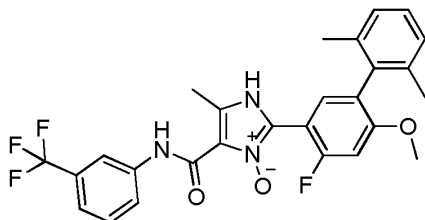
[001295] **214** was obtained via general procedure from **186-B** and **171-B**.

[001296] **LCMS:** (ESI) m/z : 497.1 $[\text{M}+\text{H}]^+$. **¹H NMR** (400 MHz, MeOD-*d*₄) δ : 9.01 (d, J = 8.8

Hz, 1H), 8.21 (s, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.21-7.17 (m, 1H), 7.10 (d, $J = 7.6$ Hz, 2H), 3.88 (s, 3H), 2.60 (s, 3H), 2.00 (s, 6H).

Synthesis of 215

[001297] **Step 1: Synthesis of 2-(4-fluoro-6-methoxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-5-methyl-4-((3-(trifluoromethyl)phenyl)carbamoyl)-1H-imidazole 3-oxide (215)**



[001298] was obtained *via* general procedure from **125-B** and **171-B**.

[001299] **LCMS:** (ESI) m/z : 514.2 $[M+H]^+$. **1H NMR** (400 MHz, MeOD- d_4) δ : 8.21 (s, 1H), 7.99 (d, $J = 8.4$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.53 (t, $J = 8.0$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.19-7.13 (m, 2H), 7.09 (d, $J = 7.2$ Hz, 2H), 3.84 (s, 3H), 2.69 (s, 3H), 2.03 (s, 6H).

EXAMPLE 2

Biological activity of compounds of the invention

ACSS2 cell-free activity assay (Cell-free IC_{50})

15 [001300] The assay is based on a coupling reaction with Pyrophosphatase: ACSS2 is converting ATP+CoA+Acetate $\Rightarrow$ AMP+ pyrophosphate + Acetyl-CoA (Ac-CoA). Pyrophosphatase converts pyrophosphate, a product of the ACSS2 reaction, to phosphate which can be detected by measuring the absorbance at 620 nm after incubation with the Biomol green reagent (Enzo life Science, BML-AK111).

20 Cell-free IC_{50} determination:

[001301] 10nM of human ACSS2 protein (OriGene Technologies, Inc) was incubated for 90 minutes at 37C with various compounds' concentrations in a reaction containing 50 mM Hepes pH 7.5, 10 mM DTT, 90 mM KCl, 0.006 % Tween-20, 0.1 mg/ml BSA, 2 mM $MgCl_2$, 10 μ M CoA, 5 mM NaAc, 300 μ M ATP and 0.5U/ml Pyrophosphatase (Sigma). At the end of the reaction, Biomol Green
25 was added for 30 minutes at RT and the activity was measured by reading the absorbance at 620nm. IC_{50} values were calculated using non-linear regression curve fit with 0% and 100% constrains (CDD Vault, Collaborative Drug Discovery, Inc.).

ACSS1 cell-free activity assay (Cell-free IC_{50})

30 [001302] The assay is based on a coupling reaction with Pyrophosphatase: ACSS1 is converting ATP+CoA+Acetate $\Rightarrow$ AMP+ pyrophosphate + Acetyl-CoA (Ac-CoA). Pyrophosphatase converts

pyrophosphate, a product of the ACSS1 reaction, to phosphate which can be detected by measuring the absorbance at 620 nm after incubation with the Biomol green reagent (Enzo life Science, BML-AK111).

Cell-free IC₅₀ determination:

- 5 [001303] 5nM of human ACSS1 protein (MyBioSource) was incubated for 30 minutes at room temperature with various compounds' concentrations in a reaction containing 50 mM Hepes pH 7.5, 10 mM DTT, 90 mM KCl, 0.006 % Tween-20, 0.1 mg/ml BSA, 2 mM MgCl₂, 15 μM CoA, 5 mM NaAc, 300 μM ATP and 0.5U/ml Pyrophosphatase (Sigma). At the end of the reaction, Biomol Green was added for 30 minutes at RT and the activity was measured by reading the absorbance at 620nm. IC₅₀ values were calculated using non-linear regression curve fit with 0% and 100% constrains (CDD Vault, Collaborative Drug Discovery, Inc.).

Cellular Fatty-acid IC₅₀ determination:

- 15 [001304] The cellular activity of ACSS2 was measured in MDA-MB-468 cells under hypoxic conditions by tracing the incorporation of labelled carbons from ¹³C-acetate into newly synthesized fatty acids. The assay was performed using 75% charcoal stripped serum (high serum conditions).

- [001305] MDA-MB-468 cells were seeded in 12-well plates (0.35 × 10⁶ cells per well) in plating medium (Dulbecco's Modified Eagle Medium containing 25 mM D-glucose, 1 mM sodium pyruvate, 10% v/v fetal bovine serum, and 2 mM glutamine) and incubated for 24 hours under hypoxic conditions (1% O₂).

- 20 [001306] The next day, tracing medium containing DMEM (01-057-1A) containing 75% charcoal stripped serum (Biological industries 04-201-1A), 3.5 μg/mL Biotin (Sigma-Aldrich B4639), 1mM Pyruvate, 5.5mM Glucose, 0.65mM Glutamine and 0.5mM ¹³C-Acetate (Sigma-Aldrich #282014) with serial dilutions of the compounds in the range of 0.000512-1000nM were prepared. The plating medium was replaced with 1 mL tracing medium plus compounds and the cells were incubated for 5 hours under hypoxic conditions (1% O₂). Plating medium in control wells (without cells or without compounds) was replaced with 1 mL tracing medium containing 0.01% v/v DMSO.

- 25 [001307] The level of ¹³C-acetate incorporation into fatty acids (palmitate) was measured by LC-MS analysis and IC₅₀ as described below:

30 **LC-MS Analysis**

Sample Preparation for LC-MS

- a) Cells were washed twice with cold phosphate buffered saline (PBS), scraped into 0.5 mL EDTA pH 8.0, and transferred into 1.1 mL V-shaped HPLC glass tubes.
- b) The cell suspensions were centrifuged for 5 minutes at 400 × g, 4 °C and the supernatants were removed.
- 35 c) Cell pellets were frozen at -80 °C.

Saponification Method

- d) Cell pellets were resuspended in 0.2 mL of 80% v/v ethanol in water containing 0.02 M NaOH in 1.1ml glass (v-bottom) HPLC vials.
- e) The vials were closed tight and incubated at 66 °C for 60 minutes.
- f) Acetonitrile containing 2% v/v formic acid (150 µL) was added to each vial and the mixtures were transferred to Eppendorf tubes for centrifugation at $17\,000 \times g$ for 20 minutes.
- g) Supernatants were transferred to LC-MS vials.

LC-MS Fatty Acids Assay

[001308] The relative palmitate concentration was measured by LC-MS in reconstructed selected ion monitoring (RSIM) mode and negative ion mode. Samples were analyzed on a Phenomenex Kinetex 2.6 µm XB-C18 150 × 2.1 mm column at 45 °C (0.4 mL/minute flow rate) using:

- a) A gradient from 15% A/85% C to 100% C for 0 to 2 minutes (A: water containing 5% v/v acetonitrile, 10 mM ammonium acetate, and 10 mM acetic acid; C: a mixture of 50% v/v acetonitrile and 50% v/v methanol).
- b) Isocratic flow (100% C) for 2 to 5 minutes.
- c) Equilibration in isocratic conditions (15% A/85% C) for 5 to 8 minutes.

[001309] Palmitate was eluted at approximately 3.4 minutes.

Data Analysis

[001310] The percent inhibition was calculated relative to the sample without compound and after background deduction. IC₅₀ values were calculated using non-linear regression curve fit analysis with 0% and 100% constraints (CDD Vault, Collaborative Drug Discovery, Inc. or GraphPad Prism).

[001311] The inhibitory activities of each compound against ACSS2 in MDA-MB-468 cells under high serum conditions, as determined by ¹³C-acetate incorporation into fatty acids (palmitate), are presented in Table 2.

Results:

[001312] The results are presented in Table 2 below:

Table 2. Biological results for compounds of the invention

Compound Number	ACSS2 Biochemical IC ₅₀ (nM) ^(a)	ACSS1 Biochemical IC ₅₀ (nM) ^(a)	Cellular Fatty-acid IC ₅₀ High Serum MDA468 (nM) ^(b)
100	+++	Inactive	+++
101	+++	Inactive	++
102	+++	Inactive	+++
103	+++	Inactive	++
104	+++	Inactive	++
105	+++	Inactive	+++
106	+++	Inactive	+
107	+++	Inactive	+++
108	+++	Inactive	++
109	+++	Inactive	+++
110	+++	+	+++
111	+++	Inactive	+

112	+++	+	+++
113	+++	Inactive	++
114	+++	+	+++
115	+++	Inactive	+++
116	+++	Inactive	+++
117	++	Inactive	N/A
118	+	Inactive	N/A
119	+++	Inactive	+++
120	+++	Inactive	+++
121	++	Inactive	N/A
122	+	Inactive	N/A
123	+++	Inactive	+++
124	+++	Inactive	+
125	+++	Inactive	+++
126	+++	Inactive	++
127	+	Inactive	N/A
128	++	Inactive	N/A
129	+++	Inactive	+
130	++	Inactive	N/A
131	+++	Inactive	++
132	++	Inactive	N/A
133	++	Inactive	N/A
134	++	Inactive	N/A
135	+++	Inactive	++
136	++	Inactive	N/A
137	+++	Inactive	+
138	+	Inactive	N/A
139	+	Inactive	N/A
140	++	Inactive	N/A
141	+	Inactive	N/A
142	+++	Inactive	+
143	+++	Inactive	++
144	+	Inactive	N/A
145	+	Inactive	N/A
146	+++	Inactive	+++
147	++	Inactive	++
148	+	Inactive	N/A
149	+++	Inactive	+++
150	++	Inactive	N/A
151	+	Inactive	N/A
152	++	Inactive	N/A
153	+	Inactive	N/A
154	+	Inactive	N/A
155	++	Inactive	N/A
156	++	Inactive	N/A
157	+++	Inactive	+
158	+	Inactive	N/A
159	++	Inactive	N/A
160	++	Inactive	N/A
161	+++	Inactive	N/A
162	+++	Inactive	N/A
163	+	Inactive	N/A
164	+++	Inactive	N/A
165	+++	Inactive	N/A
166	+	Inactive	N/A
169	+++	Inactive	+++

170	+++	Inactive	N/A
171	+++	Inactive	+++
172	+++	Inactive	+++
173	+	Inactive	N/A
174	++	Inactive	+
175	+++	Inactive	+++
176	+++	+	+++
177	+++	+	+++
178	+++	+	+++
179	++	Inactive	+
180	+++	+	+++
181	+++	+	+++
182	+++	Inactive	+++
183	+++	Inactive	+
184	+++	Inactive	+++
185	+++	+	+++
186	+++	Inactive	+++
187	+++	Inactive	++
188	++	Inactive	N/A
190	+++	Inactive	+++
191	+	Inactive	N/A
192	+++	+	++
193	+	Inactive	N/A
194	++	Inactive	N/A
195	+	Inactive	N/A
196	+++	Inactive	+++
197	+++	Inactive	+
198	+++	Inactive	+
199	+++	Inactive	++
200	+	Inactive	N/A
201	+++	Inactive	+++
202	+++	Inactive	+
203	+++	Inactive	+
204	+++	Inactive	+
205	+	Inactive	N/A
206	+	Inactive	N/A
207	+++	Inactive	+
208	++	Inactive	N/A
209	++	Inactive	N/A

a) +++ <1nM
 ++ >1nM and <30nM
 + >30nM

b) +++ <20nM
 ++ >20nM and <50nM
 + >50nM

N/A Not Available

[001313] As noted in Table 2 above, the compounds according to this invention are highly potent and selective ACSS2 inhibitors with potencies reaching sub-nonoMolar IC₅₀s in ACSS2 biochemical assay and inactive in ACSS1 biochemical assay, the closest homolog of ACSS2. The compounds are also very active in inhibiting ACSS2 in cellular assays that measure incorporation of ¹³C-Acetate into

fatty-acids in MDA-MB-468 cells, with IC_{50} s in the low nM range. Overall, the compounds of this invention are highly potent and selective ACSS2 inhibitors both in biochemical and cellular assays.